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PLUTONIUM IN MAN: A TWENTY-FIVE YEAR REVIEW*

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PLUTONIUM IN MAN: A TWENTY-FIVE YEAR REVIEW*

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DEDICATION

This review is dedicated to the memory of Dr. Burris B. Cunningham, Professor of Chemistry, University of California at Berkeley and Senior Staff Scientist of the Department of Chemistry, University of California, Lawrence Radiation Laboratory, who with L. B. Werner first prepared plutonium in pure form and who developed on a microchemical scale the chemical techiques that were later used in the purification of large quantities of plutonium. I remember with pleasure and appreciation many conversations with Dr. Cunningham on matters of plutonium and actinide chemistry.

ABSTRACT: Urinalysis was the method chosen to monitor internal Pu contamination of the chemists who separated the first batch of reactor-produced Pu in late 1943, and it is still the only way of detecting exposure to ^{239}Pu. In order to determine the relationships between urinary excretion and body Pu content, 18 persons (15 over the age of 45) were injected in 1945 and 1946 with tracer doses of ^{239}Pu. The original data have been collected and critically reviewed and re-analyzed in this paper.

Early tissue distribution. Four to 17 days after injection, human soft tissues (other than blood and liver) contained as much as 20% of the Pu dose. Five to 15 months after injection the average liver Pu content was 31% of the dose for three cases with presumably normal liver function. Data were collected on weights of fresh human bones and the intraskeletal distributions of ^{226}Ra and ^{90}Sr in man, ^{226}Ra, ^{239}Pu, and ^{241}Am in dogs, and ^{90}Sr and ^{241}Am in monkeys. Weight relationships of individual bones and their fractional radionuclide contents were used to convert Pu concentrations in small-bone samples to Pu in the whole skeleton. Four to 457 days after injection total skeletal Pu ranged from 38% to 65% of the dose, with a mean of 49% for the seven cases judged to have most nearly normal livers and skeletons.

Transport and excretion. Pu has been shown to be transported in blood combined with transferrin, the iron-transport protein, and to be stored in the liver in association with stored iron. Examination of animal data and the individual medical histories with particular attention to clues about the status of iron metabolism suggested the following:

After being bound to transferrin, Pu traces the behavior of the carrier protein. The early phases of Pu transport which are apparently associated with extra-cellular fluid mixing, were prolonged in those individuals suffering from circulatory impairment.

Maximum urinary Pu excretion coincided with the earliest phase of Pu transport (before the bulk of Pu was protein-bound). Minimum urinary excretion coincided with the time of maximum Pu-transferrin binding. These observations were taken to mean that some Pu can be filtered by the kidney in the form of a low-molecular-weight chelate. Urinary Pu excretion was reduced by one-half in those persons who were anemic, presumably because of their more efficient Pu-transferrin binding.

Early fecal excretion of Pu apparently represents secretion in bile and other digestive juices. Fecal excretion was reduced by one-half or more in those persons whose gastrointestinal tracts were judged not to be normally stimulated (those on restricted diets and one case of hepatitis).

Renal clearance increased from 1.8% to 8.1% of circulating Pu and fecal clearance rose from 2.2% to 6.8% of circulating Pu between the sixth and nineteenth days after injection. It is suggested that some Pu may be lost by desquamation of cells containing Pu (especially intestinal epithelium), or that some Pu is excreted by both the kidney and gastrointestinal tract during catabolism of the protein moiety of Pu-transferrin, or both.

Excretion curves. Semilogarithmic curves of Pu disappearance from plasma and daily Pu excretion were prepared for each individual case. So-called normal human Pu plasma and excretion equations (sums of

exponentials) were constructed from the mean half-times and intercepts for the individual cases. All cases were included in the mean half-times -- rates were apparently not affected by the individuals' various illnesses. Only the intercepts for those persons for whom a particular function was judged to be within normal limits were included in the mean intercepts -- urine intercepts were reduced by anemia or kidney dysfunction, and fecal intercepts were reduced by dietary restriction or liver malfunction.

Daily Pu excretion rates and total cumulative Pu excretion predicted from these exponential equations were slightly greater than predicted from the power functions of Langham et al. (1951), chiefly because only data from normally functioning excretory systems were included in the exponential coefficients, but also because the fecal excretion assumed in the model presented here is significantly higher than in other models.

Proposed metabolic model. Turnover of Pu in bone and soft tissues, storage of Pu in liver of the dog and pig, and storage of iron in man were reviewed. At tracer levels of Pu (defined as the absence of gross damage during the time of observation) net loss of Pu from soft tissues and bone exceeds whole-body Pu loss, indicating continuous accumulation of Pu in the liver. Average soft-tissue release half-time was estimated to be no less than 480 days, and bone-surface turnover for the whole adult human skeleton was estimated to be about 5% per year. For an individual on a diet adequate in iron and with normal iron stores, this model predicts that bone and liver will contain equal amounts of Pu 15 years after exposure. This model fits the available data from

animals and for occupational Pu exposures, and supports the view of Mays et al. (1970) that the liver rather than the skeleton may be the critical organ for Pu.

INTRODUCTION

Plutonium was recognized as potentially dangerous even when the total amount of Pu in existence was only a few milligrams. If the Metallurgical Laboratory efforts were successful, enormous amounts of plutonium--hundreds of times the world supply of radium--would be produced. The urgent need for biological studies of Pu was appreciated and these were begun as soon as Pu could be spared from essential chemical investigations. On November 4, 1943, Dr. Arthur H. Compton announced to the Metallurgical Laboratory (Plutonium) Project Council that the Clinton pile had "taken off,"* and plutonium was being produced in weighable quantities.[1] By January 19, 1944, 0.5 g of Pu had been separated,[2] and three weeks later, on February 8, 1944, Hamilton's group at Berkeley received 11 mg to begin tracer studies in rats.[3]

With only preliminary results of the initial tracer studies in hand, Dr. Robert Stone,[4] Director of the Metallurgical Laboratory Health Division, wrote in early 1944: "I must emphasize the serious health hazard of plutonium itself. Before it was available, we regarded it as similar from a radiation standpoint to the alpha-emitting decay products in the radium series. Now we find its behavior places it among substances that will remain in the lungs for long periods if not indefinitely. That which enters the blood probably becomes fixed in bone. The only safe procedure is to see that none of it is inhaled or ingested."

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*The verbatim entry in the Minutes of the Project Council[1] is "Nov. 4, 1943--Clinton pile takes off--production now on experimental scale."

Despite precautions, Pu contamination of laboratories and personnel at several Metallurgical Laboratory installations was a chronic problem,[5,6] and one of the Health Division's pressing tasks was to devise a method of determining whether a Pu burden had been acquired. The first approach was analysis of Pu in urine,[7-9] and tracer data from rodents were used to relate Pu in urine to the body burden.* If urinalysis was to be a reliable assay for Pu in contaminated human beings, characterization of its behavior in man was essential. For this reason, 18 hospitalized persons [12 at Rochester, N.Y., and 3 each at Chicago, Ill., and San Francisco (Berkeley), California] were injected with tracer amounts of Pu in 1945 and 1946.

In May 1945, a few weeks after the first two studies of human Pu excretion were begun, a conference was held to bring together what was then known about the biology of Pu.[18] Before the conference the industrial physicians responsible for the radiological protection of the personnel at Metallurgical Laboratory installations were asked to indicate what kinds of information about Pu behavior were needed most. R. S. Stone's summary of their questions is reproduced in full as Appendix 1. Some of their requests have been partially satisfied, but we are still seeking much of the information about Pu behavior that the pioneers in this field considered necessary for the proper protection of Pu workers.

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*The rodent tracer studies and inhalation experiments (Hamilton et al.[10,11]) and attempts at Pu decontamination (Copp et al.[12]) by the Berkeley group, and the tracer and toxicity and inhalation studies in several species by Cole's group in Chicago (Finkle et al.[13], Painter et al.[14], Brues et al.[15] Bloom[16] and Abrams et al.[17]) are the foundation of our knowledge of the biological behavior of Pu. Photocopies of the unpublished laboratory reports, available at cost from the Division of Technical Information, P. O. Box 62, Oak Ridge, Tennessee, 37830, belong in the library of every student of Pu biology.

The power-function curves of human Pu excretion published by Langham et al.[19,20] which were constructed by using data from the hospital patients and excretion data from several occupationally exposed persons, provided a method of predicting Pu body content based on urinalysis. Langham's method has been reanalyzed many times.[21-25] There have been mathematical refinements, and analytical chemical and α-particle detection techniques have been greatly improved,[26,27] but the underlying assumptions are unchanged.

Pu may soon be widely used as reactor fuel. It is timely to reexamine the original data, gathered nearly 25 years ago, because meager as they are, they represent nearly all our human Pu experience. The details of the radiochemical techniques, the pertinent details of the individual case histories, and the original data are for practical purposes buried in privately printed Manhattan District and AEC project reports.* (Data for two cases had not previously been reported.) In this reexamination I have attempted to bring together under one cover as much as possible of the original detail, and to improve the usefulness of the information. Study of the behavior of Pu in each patient, rather than averages for the group, should reveal differences in their Pu metabolism (as a result of their various illnesses) that might be used to predict the behavior of Pu in healthy persons.

A retrospective study has the additional advantage of being able to draw on newer knowledge. Long-term excretion data are now available from the lower-dose dogs in the Utah experiment.[28,29] The protein that

*Few copies were printed, and many have been lost or destroyed. Photocopies of the original documents are available from TID, Oak Ridge.

binds Pu in plasma has been identified as transferrin by groups at Harwell[30,31] and Utah.[32,33] The kinetics of iron, the element normally carried by transferrin, have been worked out in detail.[34-37] Now, there is also some information on the behavior of Pu in two other large animals, the sheep[38,39] and the pig.[40-43] All these recent observations provide a framework, not available to the original investigators, in which to examine and interpret the human Pu data.

MATERIALS AND METHODS

With two minor exceptions, the data examined for this report have been published in one form or another. The following brief description of the original data sources is included chiefly to eliminate confusion about the Berkeley and Chicago cases (Cal-1, Chi-1, Chi-2, and Chi-3), for which fragmentary reports have appeared more than once. Summaries of the histories of the published cases and complete case histories of two previously unpublished cases are included as Appendix 2.

Langham et al.[19]

All the information obtained for HP-1 through HP-12 is contained in this reference, which includes medical histories, injection data, hematologic data, blood chemistry, and Pu analyses of blood, urine, feces, and biopsy and autopsy specimens. Pu analyses of urine, feces (fecal data from Cal-1 were not included), and biopsy and autopsy specimens are reported for Cal-1, Chi-1, Chi-2, and Chi-3. Pu urinalyses are reported for three occupationally exposed persons. Pu radiochemical methods are described briefly and reported in detail elsewhere.[44-46]

Russell and Nickson[18,47-53]

All the original data from Chi-1 and Chi-2 are contained in Ref. 47,

which includes case histories, injection data, hematologic examinations, and Pu analyses of urine, feces, and autopsy specimens. The remaining references contain the original data for Chi-3 and fragmentary data from the other two cases. (Additional information was obtained from E.R. Russell for Chi-3.) Pu radiochemical techniques used by the Chicago group can be found in Refs. 54-56.

Crowley et al.[57]

Most of the information obtained from Cal-1 is included in this report, which includes a brief medical history, injection data, and Pu analyses of urine, feces, blood, and biopsy specimens. Radiochemical techniques are also included. Additional information was obtained from raw data sheets, hospital records, and death certificate.

Foreman et al.[58]

This report contains all the information from a case of occupational Pu exposure (designated herein as LASL-1).* Included are Pu exposure history and Pu analyses of urine and autopsy specimens. Radiochemical techniques are described elsewhere.[26]

Hamilton et al. (unpublished)

All the information about two previously unreported cases injected by the Berkeley group Cal-2 and Cal-3, are included in Appendix 2.

Copies of all the original reports were obtained, and were compared for omissions and errors of transcription. The Pu contents of the autopsy specimens of Chi-1 and Chi-2 were originally reported as μg Pu per g tissue. These data were converted to % dose per g. The original data sheets were still available for Cal-1, and these were checked for numerical correctness. The transcription and numerical errors that were found are collected in Appendix 3.

* LASL-1 is now designated LASL-10038 by the The Los Alamos Laboratory Health Group (L. J. Johnson, private communication).

Details of the calculation of total tissue Pu or bone Pu are described in conjunction with the tabulated results of these calculations or in the Appendices. The semilogarithmic curves of Pu in blood and excreta were fitted by eye to the original data points and analyzed by standard graphic methods. Straight-line segments were fitted by the least-squares method. These are admittedly subjective procedures, but there were often so few data for each patient that machine curve fitting seemed inappropriate.

Data from the laboratory animals were obtained from published curves and tables: [dog,[28,29,59-61] sheep,[38,39] swine[40-43] and rat.[10,62,63]] Data points were read from curves by reconstructing the grid lines, measuring the distances from the horizontal and vertical origins with a millimeter scale, and calculating (as closely as this rough technique permits) the original values from the measured distances. B. J. Stover and D. R. Atherton kindly supplied original data for Pu excretion by individual dogs.

PLUTONIUM IN SOFT TISSUES

Soft tissue* specimens from five cases that came to autopsy were analyzed, and a small sampling of soft tissues was obtained during surgery in a sixth case. The analytical results are collected in Table I. Organ and tissue weights were estimated from the recorded body weight and the weight proportions of "Standard Man"[64,65] tabulated in Appendix 4. The calculated weights of tissues and organs and their total calculated Pu contents are also shown in Table I.

*Unless otherwise specified, soft tissue includes muscle; skin; connective, lymphatic, and nervous tissue; fat; glands; all organs except liver; blood and other body fluids except bladder urine, and gastrointestinal contents. Thus the whole body consists of liver, bone, and soft tissue.

Table 1. (Part 1)

Material balances of soft tissues and excreta. Six persons injected i.v. with Pu(IV) citrate, Pu(VI) nitrate, or Pu(VI) citrate

	Pu(IV) Citrate								
	HP-5, 151 days p.i.			HP-9; 456 days p.i.			HP-11; 5 days p.i.		
	Male, 56 yr.			Male, 66 yr.			Male, 68 yr.		
	% Pu/g	70.8 kg[a] wt (g)	Calc. (%) dose	% Pu/g	63 kg wt (g)	Calc. (%) dose	% Pu/g	70.8 kg[a] wt (g)	Calc. (%) dose
Liver	0.032	1,340[b]	42.8	0.0144	1,600[b]	23.0	0.0053	2325	12.3
Spleen	0.0007	184	0.13	0.0015	162	0.24	0.0048	184	0.89
Kidney	0.0002	312	0.062	0.0002	277	0.055	0.0015	312	0.47
Lung	0.0005	1,000	0.50				0.0016	1,000	1.60
Pancreas	0.0002	100	0.02	0.0002	90	0.018			
Intestines	0.00015	1,020	0.15				0.00045	1,020	0.46
Testes	0.0003	64	0.018				0.0012	64	0.077
Thyroid	0.0001	16	0.0016				0.0009	16	0.014
Adrenals	0.0004	14	0.0056				0.0022	14	0.031
Muscle	0.0002[c]	28,400	6.67	0.0002[c]	25,200	5.92	0.0002	28,400	5.68
Skin		4,950			4,410		0.0002	4,950	0.99
Residual soft tissue	0.0001[d]	23,080	2.31	0.0001[d]	22,280	2.23	0.0001[d]	22,200	2.22
Excreted[e]			5.20			16.5			2.00
Total (accounted for)			57.9			48.0			34.7
Skeleton (calc.)		10,300	42.1		9,166	52.0		10,300	65.3

Table 1. (Part 2)

Material balances of soft tissues and excreta. Six persons injected i.v. with Pu(IV) citrate, Pu(VI) nitrate, or Pu(VI) citrate

	Pu(VI) Citrate						Pu(VI) Nitrate		
	Chi-1; 160 days p.i.			Chi-2; 17 days p.i.			Cal-1; 4 days p.i.		
	Male, 68 yr.			Female, 55 yr.			Male, 58 yr.		
	76.4 kg			38.6 kg			58 kg		
	% Pu/g[g]	wt (g)	Calc. (%) dose	% Pu/g[g]	wt (g)	Calc. (%) dose	% Pu/g[g]	wt (g)	Calc. (%) dose
Liver	0.0135	2,050[b]	27.8	0.0024	1,110	2.70		1508	-
Spleen	0.0025	260[b]	0.65	0.0012	85[b]	0.10	0.0019	167[b]	0.32
Kidney	0.00038	340[b]	0.12	0.0054	190[b]	1.03			
Lung	0.00058	1,950[b]	1.13	0.0016	490[b]	0.78			
Pancreas				0.0022	60[b]	0.13			
Intestines				0.00065	555	0.36			
Testes	0.00052	66	0.034						
Thyroid				0.0034	14	0.048			
Adrenals									
Muscle	0.00025[c]	30,560	8.98	0.0006	11,310	6.79	0.0004[c]	23,200	9.28
Skin		5,348		0.0006[c]	2,320	1.39	0.00058	4,550	2.64
Heart	0.00028	382	0.11	0.00105	250	0.26			
Diaphragm	0.00023								
Lung tumor	0.0017	32	0.054						
Lymph node	0.0015	764	1.16	0.00074	390	0.29			
Ovaries				0.00094	10	0.009			
Omentum							0.0004		
Subcutaneous tissue							0.0004		
Scar tissue							0.0011		
Residual soft tissue	0.00012[d]	23,800	2.98	0.0003[d]	14,700	4.41	0.0002[d]	16,690	3.34[h]
Blood									5.66
Excreted[e]			6.74			0.70			1.19
Total accounted for			49.8			19.0			25.7
Skeleton (calc.)		9,428	50.2		7,125[i]	81.0		9,428[i]	(mid-range 42.5)

Footnotes to Table I

[a] Body weight estimated to be the mean weight of six male cases whose body weights were recorded.

[b] Measured tissue weight.

[c] Pu concentrations in muscle and skin (when not measured) were estimated to be the average of other measured soft tissues such as heart, pancreas, etc.

[d] Pu concentration of residual soft tissue was estimated to be one-half the concentration in skin and muscle.

[e] Measured totals are used when available. Excretion between the cessation of collections and deaths of HP-5 and HP-9 was estimated from extrapolation of the last available measurements and the slopes of the U and F curves of persons followed for longer times. Excreta from HP-11 were estimated to be the mean for all the other Pu(IV) citrate-injected cases.

[f] Includes 7.95%, the average Pu content of blood of the two sickest persons (HP-4 and HP-10), from whom blood samples were obtained at this time.

[g] %/g of Pu recalculated from original data.

[h] Includes 3.25% estimated from the tissues of Chi-2, and HP-11.

[i] Chi-2 was emaciated; her skeleton was assumed to be the average reported by Mechanik[66] for slightly built females. Cal-1 had lost 15 lb during his illness; his skeletal weight was calculated from his body weight in good health, 64.8 kg.

In order to estimate total body Pu as closely as possible, it was necessary to make some assumptions about tissues that were not sampled; for example, a correction was made for the unsampled abdominal and thoracic organs of Cal-1. When skin and muscle were not measured, the average Pu concentrations of other tissues such as heart, diaphragm, or pancreas were used. Details of these estimated values appear in the footnotes to Table I. In every instance it was necessary to estimate the Pu content of the soft-tissue remainder, consisting of fat, fascia, nerve, tendon, etc. The total weight of the soft-tissue remainder was calculated by subtracting from the body weight the sum of the weights of the sampled tissues and the calculated skeletal weight. For Cal-1 the Pu concentrations in omentum and subcutaneous tissue were almost as great as that in skin. The Pu concentration in the fat sample obtained from Chi-2 was the same as that in intestine, muscle, or tumor. The fat sample obtained from Chi-1 had a Pu concentration about one-fifth that in muscle or skin. Based on these observations, the average Pu concentration in the soft-tissue remainder was estimated to be one-half that in the average of muscle and skin.

The calculated Pu content of the soft tissues of the six human beings (shown in Table I) is considerably greater than has been reported in the dog. About 3% was present in soft tissues of the beagle 22 days after intravenous injection.[28] It was possible to calculate from the data of Smith et al.[42] that the soft tissues of yearling miniature swine contained as much as 25% of the injected dose 6 days after intravenous injection of Pu(IV) citrate.

In their original report of Pu toxicity in dogs Painter et al.[14] included a tabulation of Pu concentrations in a large number of soft tissues of individual dogs. Complete excretion data and periodic blood samplings were also reported for two of these dogs that died 15 or 16 days after intravenous injection of Pu(VI) citrate. These data provided a means of testing the accuracy of the balance-sheet method of calculating whole-body Pu distribution in large animals when only a small number of tissues have been sampled.

The recorded body weights of the individual dogs (corrected for radiation-induced weight loss of 10% to 16%) and the weight proportions of the beagle[67-69] were used to estimate individual tissue weights. The sums of the Pu analyses of excreta, the estimated Pu content of the skeleton (calculated as described in the next section) and of the liver and soft tissues were 94% and 99% for the two dogs--an encouraging result. Early soft-tissue distribution of Pu in man is compared in Table II with Pu distribution in dog, pig, and rat.

The movement of Pu out of the soft tissues of the six human cases is shown in Fig. 1. Extrapolation of the initial steep portion of the curve indicates that about 24% of the injected Pu was present in these tissues (and their contained blood and extracellular fluid) 24 hours after injection. The equation of the exponential curve in Fig. 1 is

$$\text{Soft-tissue Pu} = 8\%\ e^{-0.096t} + 16\%\ e^{-0.0014t}, \qquad (1)$$

where t is days^{-1}. The initial rate of Pu loss from the soft tissues of the toxicity dogs and from rats[10,62] appears to be about the same as estimated in Fig. 1 for man ($T_{1/2}$ = 7.2 days). Although there are no detailed reports of the amount of Pu in the soft tissues of normal dogs

Table II. Early Distribution of Intravenously Injected Pu (as % of injected dose) in Soft Tissues of Man, Dog, Rat and Pig.[a]

	Man	Dog	Rat	Pig
Form of Pu	Pu(IV) citrate	Pu(VI) citrate	PuO_2Cl_2	Pu(IV) citrate
Days p.i.	4 to 5	15 to 16	4	6
Liver	35.3[b]	29.6	27.7	14.0
Spleen	0.60	0.71	0.40	0.24
Kidneys	0.47	0.33	2.08	0.20
Lung	1.60	0.12	0.15	
Pancreas	0.13	0.015		
G.I. tract	0.46	0.23		
Testes	0.077		0.15	0.10
Thyroid	0.014	.0010		
Adrenals	0.031	.0085		0.0017
Muscle	7.48	7.38	1.50	
Skin	1.82	1.33	1.68	
Heart	0.26[c]	0.023	0.13	
Lymph tissue	0.29[c]	1.59		
Brain		0.004	0.011	
Thymus		0.015		
Blood	6.80	0.21	0.62	
Remainder	2.78	0.39	3.48	
Ovaries	.009[c]	0.002		

[a]Data sources: man, average of HP-5, Chi-1, and Cal-1, see Table I this paper; dog, Pu data average of dogs #33 and #42, Tables 25 and 26[14]; tissue and organ weights[67-69]; rat[10]; pig[42].
[b]Average of HP-5 and Chi-1 only.
[c]Source: Chi-2, 17 days p.i.; see Table I.

or pigs shortly after injection, there is some indirect evidence from the Utah experiments that Pu continued to be deposited in the liver and bone during the first week to 10 days after injection. Thus, the amount of Pu initially in the soft tissues (at least 20% can be accounted for in the blood volume alone) was substantially more than the 3% measured at 22 days.[28] Most of the Pu that leaves the soft tissues of either dog or man does not leave the body, but is redistributed to the liver and skeleton. It appears that most of the Pu (at least 80%) originally in the soft tissues of the dog is sufficiently labile to participate in this redistribution. On the other hand, nearly two-thirds of the Pu initially found in the soft tissues of man seems to be more firmly bound.

The two low-dose dog studies yield comparable long-term rates of removal of Pu from soft tissues. The half-times of the soft-tissue curves ranged from 800 days for lung to 1050 days for skeletal muscle[59] through the first 4 years post injection, and from 950 days for spleen to 1500 days for kidneys of low-dose dogs followed for 8 years.[60] A half-time of 900 days can be calculated for Pu in total soft tissue of the beagle from data of Stover et al.[28] Two of the three human cases who survived more than 150 days and who characterize the slower Pu phase of loss were suffering from diseases associated with tissue wasting. It is likely, therefore, that the curve fitted to their data ($T_{1/2}$ = 480 days) is too steep. A more appropriate representation of long-term loss of Pu from human soft tissues is probably that shown for the soft tissues of the low-dose dogs.

Two general impressions emerge: first, during the first few days after injection the soft tissues of the human beings had higher Pu concentrations and contained greater total amounts of Pu than has been observed for two other moderate-sized species; and second, a larger fraction of the Pu initially present in the soft tissues of man remained in those tissues for a long time.

PLUTONIUM IN THE SKELETON

The Pu content of the entire skeleton has been measured in several species: mouse,[13] rat,[10,13,62] dog,[61] and pig.[42] The results are consistent--about one-half of parenterally administered complexed monomeric Pu is initially deposited in the skeleton. For many reasons the Pu content of a whole human skeleton has not been measured. In the original report of the human Pu cases total skeletal Pu was calculated by a straightforward method--the mean Pu concentration of all the bone samples was multiplied by 10 kg, the estimated average bone mass of "Standard Man",[64] yielding a calculated total skeletal Pu of 65%.

Since 1951, when the human Pu cases were reported, Pu has been measured in all the individual bones of the dog,[61] and in several bones of the rat,[70] rabbit,[71] and pig.[43] The results are all the same: vertebrae, ribs, and sternum--the bones sampled in the human cases--have higher initial Pu concentrations than the skeleton as a whole, which means that the total skeletal content of the human Pu cases was probably overestimated.

Balance-sheet method

The first method of estimating skeletal Pu uses the material balance described in the section on soft tissues,

$$Pu_{sk} = 100\% - (Pu_l + Pu_{st} + Pu_e), \quad (2)$$

where Pu_{sk}, Pu_l, Pu_{st}, and Pu_e are the percent of injected dose in the skeleton, liver, soft tissues, and excreta, respectively. Equation (2) assumes that the calculated values for Pu_l and Pu_{st} are accurately known.

The maximum Pu_{sk}--that is, the amount of Pu left over after accounting for Pu_l, Pu_{st}, and Pu_e of each individual human Pu case--appears in the bottom row of Table I. Pu_l was not measured for Cal-1, so a possible range of Pu_{sk} shown for him used as limits the highest and lowest measured values of Pu_l from three other cases that were considered to have approximately normal livers.

The mean Pu_{sk} for all six cases, regardless of their health status, was 55%--10% less than was originally calculated. Some of the reasons for this change are that the following have now been accounted for: (a) excretion between the end of collections and death; (b) Pu in all soft tissues whether samples or not; and (c) Pu remaining in the circulation of the two cases from whom tissue samples were obtained 4 to 5 days after injection.

As Langham et al.[19] pointed out, the livers of two of the cases were highly abnormal. The liver of Chi-2 had been almost completely replaced by tumor. Her Pu_l was less than 2%, and her calculated Pu_{sk} was 81%. When case HP-11 was injected, he was dying of hepatic failure (cirrhosis resulting from chronic alcoholism and malnutrition), and his liver was only partially functional. His Pu_l was 12%, and his calculated Pu_{sk} was 65%. The range of calculated Pu_{sk} was 42% to 52% and of Pu_l 23% to 43% for the three cases whose livers were presumably healthy. With respect to Pu kinetics, it would appear that liver and bone compete for Pu, and that when liver function is impaired, accumulation of Pu

by bone is increased and makes up the difference. If the two cases with impaired liver function are omitted and only the three cases with presumably normal livers are considered, the mean Pu_l is 31.2%, and the mean Pu_{sk} is 47%--nearly 18% less than originally estimated by Langham et al.[19]

Ponderal method

The second approach to estimation of Pu_{sk} has been called the "ponderal method" by Marei and Borisov.[72] Total skeletal radionuclide is calculated from the concentration in individual bones and from (a) the ponderal (weight) relationships between individual bones and the whole skeleton, and (b) the distributional relationships between the radionuclide in individual bones and in the entire skeleton according to the equation

$$Pu_{sk} = \frac{BW \times fsk \times fb_i \times (Pu_i)}{fr_i}, \qquad (3)$$

where BW is the body weight, fsk is the fraction of the body weight contributed by the skeleton, fb_i is the fraction of the skeletal weight contributed by the individual bone i (or a group of similar bones), (Pu_i) is the measured Pu concentration (%/g) in bone i, and fr_i is the fraction of the skeletal radionuclide contributed by bone i. All weights are in grams. Body weight and (Pu_i) are measured quantities; fsk, fb_i, and fr_i must be evaluated independently.

Plutonium concentration in bone samples

Bone specimens were obtained from the five autopsied cases and from four other cases during biopsies or surgery. Results are shown in Table III. The bone samples of the two Chicago cases and the three

Table III. Summary of Pu Concentration in Human Bone Samples (Pu_i) and Calculation of Total Pu in the Sampled Bones and Total Skeleton Based on Intraskeletal Distribution of Ra and Sr in Man, Am in Monkey and Pu in Dog.[a]

Case	Bone sampled	(Pu_i) %/g	Wt (g) (calc.)	% of Pu (calc.)	% of Pu in total skeleton, based on[a] Ra, Sr man	Am monkey	Pu dog
HP-5	Vertebra	0.0071	1916	13.60	56	47	38
	Rib (whole)	0.0070	639	4.47	36	76	38
	Sternum	0.0050	144	0.72	40	48	40
HP-9	Vertebra	0.0080	1705	13.64	56	47	39
	Rib (whole)	0.0038	568	2.16	17[b]	37	18[b]
HP-11	Vertebra	0.0070	1916	13.41	55	46	38
	Rib (whole)	0.0068	639	4.34	35	74	37
	Sternum	0.0096	144	1.38	77	92	77
HP-12	Radius end	0.0187	126	2.36[c,d]		103	
	Patellae	0.0109	72	0.78[d,e]		162	
Chi-1	Rib[f]	0.0079	689	5.44	44	92	46
	Sternum	0.0047	156	0.73	40	49	40
Chi-2	Rib[f]	0.0200	442	8.84	71	150	76
Cal-1	Rib[f]	0.0081	584	4.73	38	80	40
Cal-2	Femur	0.0436	286	12.47	>100g		
Cal-3	Femur	0.0031	1946	6.09	57		

[a]See text and appendix 7.
[b]Omitted from average.
[c]Ends of radii and ulnae of adult rhesus monkeys contribute 33% of the whole-bone wet weight.
[d]P. W. Durbin (unpublished).
[e]Measurement of patellae separate from leg bones was made only for Sr in the monkey and represented 0.48% of the skeletal burden.
[f]Results published for subdivided samples. See appendix 5 for reconstruction of whole bone.

California cases were subdivided into several parts, e.g., periosteum, marrow, spicules, cortex, etc. Tabulations of fresh weights of human bones and radionuclide contents of human and animal bones were all reported in terms of whole bone, which includes periosteum, articular cartilage, and marrow. In order to make use of the published bone weights and intraskeletal radionuclide distributions, it was necessary to reconstruct the whole-bone samples from their reported parts. Both the weights of the bone subsamples and their Pu concentrations were published for the Chicago cases. Much of the original California data was still in our Laboratory files. The samples were all small. If we assume that the original investigators tried to avoid sample losses, then whole-bone weight can be calculated as the sum of the subsamples, and (Pu_i), the average Pu concentration in the whole bone, can be calculated from

$$(Pu_i) = \Sigma \frac{W_i \times (Pu_i)}{\Sigma W_i}, \qquad (4)$$

where W_i and (Pu_i) are the weights and Pu concentrations, respectively, of the individual subsamples. Details of the calculations are shown in Appendices 2 and 5.

Fractional weight of the skeleton

A literature search revealed 29 complete dissections of fresh skeletons from weighed cadavers[66,73-78] (see Appendix 6). The best estimates of fsk for the human skeleton are 14.6±3%* and 11.9±1.7% of the body weight for the adult male and female, respectively. The weights of the individual skeletons of the Pu cases were calculated and appear at the bottom of Table I.

* Mean ± S. D.: S. D. $=[\text{summation } (\text{dev})^2/(n-1)]^{1/2}$

Fractional weight of the bones

Three of the early investigations[66,74,75] included the weights of all the freshly dissected bones of the human skeleton. Volkmann[75] and Mechanik[66] reported data for several individuals and included complete descriptions of methods and experimental conditions. The average weights and weight fractions were calculated for each bone or group of similar bones from their raw data, and the results are collected in Appendix 6. These dissections were the work of skilled anatomists who cleaned the bones carefully and completely. These dissections were probably much more thorough than might be expected of the busy autopsy surgeons who removed the bone specimens from the human Pu cases. Questions might also be raised about the accuracy of the old balances and about possible differences between the size and proportions of the earlier skeletons and those of middle-aged persons in the United States in 1945.

An unpublished paper by Marei and Borisov[72] (made available by the late J. L. Rivera) provided at least partial answers to some of these problems. They dissected seven male and six female cadavers of persons who had died near Moscow in 1967. Groups of bones were weighed on modern equipment, and drying was avoided. Their dissections included only "careful preliminary removal of soft tissue." Skeletal weight fractions, fb_i, calculated from the data in the two old investigations, agree completely with each other. However, the modern skeletons are about 2,000 g heavier, and the fb_i of the skull and vertebral column are somewhat greater than those calculated from the earlier dissections. Not only did the new data take care of the problems of experimental conditions and modern vs. earlier skeletons, but the dissection tech-

niques were not so precise--just what was needed. Marei and Borisov's[72] data for fresh weights of individual bones and the fb_i's calculated from them are also included in Appendix 6.

The fb_i's derived from the Marei and Borisov[72] data were multiplied by the calculated weights of the skeletons of the Pu cases to obtain an estimate of the wet weight of each sampled bone or group of bones as shown in Table III.

Intraskeletal distribution of Pu

Fractional distribution of Pu introduces the greatest uncertainty into the ponderal calculation, because it cannot be evaluated directly. Distribution of Pu in all the individual bones has been measured only in the dog.[61,79] The use of the dog data to describe Pu distribution in the human skeleton has two serious disadvantages. First, because the dog is a quadruped, the fb_i's of many of the bones differ from those of the same bones of man; for example, those of the skull, hind limb bones, and pelvis are too small, and those of the ribs, sternum, and mandible are too large. These differences in weight distribution. and presumably also the functional differences resulting from different patterns of weight bearing, are likely to be reflected in the radionuclide distributions in the skeletons of man and dog. The second disadvantage is a consequence of the design of the dog experiments. All the measured dog skeletons were either (a) those of high-dose dogs that lived long enough after injection to have accumulated variable amounts of damage to bone or liver, or both, or (b) those of low-dose dogs that lived for several years after injection, long enough to have remodeled a great deal of bone.

The distribution of ^{241}Am, an actinide element with principal valence +3 and chemical properties qualitatively similar to those of Pu, has been measured in the bones of the monkey (P. W. Durbin, M. H. Williams, and N. Jeung, unpublished). The ^{241}Am studies in the monkey (summarized in Appendix 7) satisfy the requirements of full skeletal maturity, short postinjection interval, and absence of bone damage. However, the proportions of the monkey skeleton are not the same as those of man--the monkey has a relatively larger torso and heavier forelimbs, and a relatively smaller pelvic girdle and smaller hind limbs. There are therefore some uncertainties in applying the monkey data to the human case.

The skeletal distribution of ^{241}Am has also been determined in the dog,[80] and the results compare reasonably well with those for the same element in the monkey and with ^{239}Pu in the dog. (These data are reproduced in Appendix 7.) At least one alkaline earth element has been studied in each of these animal species, and two have been measured in man. ^{226}Ra has been measured in the dog skeleton;[79] the distribution of ^{90}Sr has been determined in the monkey skeleton,[81] and data were found from which it was possible to calculate the distribution of ^{226}Ra and ^{90}Sr in the human skeleton.[82-84]

For all practical purposes, the human data are unpublished, so it is appropriate to describe them and the way in which they were manipulated to obtain fractional skeletal isotope distributions.

^{226}Ra in human bones

Evans's group at the Massachusetts Institute of Technology exhumed and measured the Ra content of the bones of a large number of exposed

persons.[82,83] However, only two cases approached satisfying the requirements of full skeletal maturity at exposure, a relatively brief interval between exposure and death, and a long enough burial time to permit nearly complete soft-tissue decomposition and drying. Case MIT-01-434 was 48 years old at exposure and died 2 years after cessation of exposure.[83] Case MIT-01-501 was 68 years old when exposed, and died 8 years after cessation of exposure.[83] Both drank a ^{226}Ra preparation for about 3 years. The data were reported as the ratio of isotope fraction to bone-mass fraction, fr_i/fb_i. For the purposes of this paper it was necessary to convert to fr_i by multiplying fr_i/fb_i reported for each bone (or group of bones) by the appropriate fb_i taken from the data of Ingalls.[85]*

^{90}Sr in human bones

In the course of their investigations of ^{90}Sr in fallout, Kulp and Schulert[84] analyzed ^{90}Sr in the individual bones of two groups of composited human skeletons. There were seven skeletons (average age 76 years) in the first group, and thirteen skeletons (average age 69 years) in the second group. All the individuals died during 1957 only 3 years after ^{90}Sr began to be present in the environment. The analytical results were reported as μμCi ^{90}Sr per g Ca in individual bones. Some assumptions about the composition of the samples were needed in order to make the conversion to fraction of skeletal ^{90}Sr. The bone ash was

*Ingalls's[85] data were used because the weights he reported were for bones of middle-aged to elderly white males. The bones were macerated and externally cleaned but not fat-extracted, and their composition was assumed to be most like these exhumed skeletons. The original data were inaccessible, because the MIT records were being moved to Argonne National Laboratory. Use of the measured weights of the individual bones would yield more accurate intraskeletal ^{226}Ra distributions.

assumed to be 40% Ca. Female skeletons were assumed to occur in the same proportions in these samples as in Kulp and Schulert's[85] main collection of ashed skeletons, about one in ten, and it was also assumed that the sample contained 10% Negro skeletons. With these assumptions, Trotter and Peterson's[86] data were used to calculate an average skeleton ash weight of 2190 g. Their data on the ash weights of individual bones of white males more than 60 years old were used to calculate fb_i, and the following equation was solved for each analyzed bone:

$$\mu\mu Ci\ ^{90}Sr/bone = (\mu\mu Ci\ ^{90}Sr/g\ Ca) \times (0.4\ g\ Ca/g\ ash) \times (2190\ g\ ash) \times (fb_i\ ash).$$

The ^{90}Sr content of whole long bones was reconstructed from the data (reported as mid-shaft, elbows, knees, etc.) by using the ash-weight proportions measured for epiphyses and diaphyses of the long bones of rhesus monkeys (P. W. Durbin, M. H. Williams, and N. Jeung, unpublished). Although the other requirements were met--the individuals were adults, and skeletons were measured shortly after exposure to a low dose--the large analytical errors because of the low ^{90}Sr levels introduce some uncertainties.

These two admittedly crude estimates of the skeletal distributions of ^{226}Ra and ^{90}Sr in man (shown in Appendix 7) agreed surprisingly well. They also agreed generally(despite some specific species differences) with the distributions of ^{226}Ra and ^{90}Sr in the animals and qualitatively with the distributions of the actinide elements in the animals. The existence of a common pattern of intraskeletal distribution of such seemingly dissimilar elements is not too surprising, because the initial site of deposition of all the bone-seeking elements is on

anatomical surfaces and deposition is probably related to vascularization and blood flow.[87]

The last three columns in Table III contain the solutions of Eq. (3) for each available bone specimen, based on fr_i taken from (a) alkaline earths in man, (b) ^{241}Am in the monkey, or (c) ^{239}Pu in the dog. The sources of error in total skeletal isotope calculated from Eq. (2) are examined for an ideal case in Appendix 8. An average Pu_{sk} was calculated for the cases in which Pu concentration had been measured in more than one bone and these appear in Table IV. The Pu_{sk} of each human case calculated from Eq. (3) is compared in Table IV with the results obtained from the material balance. The best agreement between the two methods of calculating Pu_{sk} was achieved when fr_i was based on the alkaline earth distribution in man.

The Pu_{sk} calculated was greater than 100% for HP-12, an obvious impossibility. The bone specimens analyzed in that case were fragments removed from the radius head and patella during surgical repair of comminuted fractures. Surgery occurred 21 days after the bones were fractured and 5 days after the Pu injection. Callus formation and resorption of damaged bone were probably already well under way when the Pu was injected. Van Middlesworth[88] showed that Pu uptake in a healing fracture was as much as four times as great as in the contralateral normal bone when partial healing had been permitted to occur before the Pu injection.

The small piece of femoral metaphysis from Cal-2 (designated as cortex) was evidently not normal. Even assuming uniform skeletal Pu

Table IV. Comparison of Total Skeletal Pu Calculated by Material Balance and by Ponderal Method by Use of Intraskeletal Distributions of Various Radionuclides in Man, Monkey and Dog.[a]

Case	Days p.i.	Injected Pu (%)			
		Material balance	Average of Ponderal Calculations based on,		
		Table 1	Ra, Sr, Man[a]	Am, Monkey[a]	Pu Dog[a]
HP-12[c]	4			132	
Cal-1	4		38		39
Cal-3	4		57		
HP-11[d]	5	65	56	71	51
Chi-2[d]	17	81	71	150	73
HP-5	151	42	44	57	38
Chi-1	160	49	42	70	43
HP-9	456	52	56	42	39
Cal-2[e]	7		>100		

[a]See text and appendix 7.

[b]Pu in dog sternum, Stover et al., in press.

[c]Fragments from healing fractures.

[d]See text for comments on hepatic function of HP-11 and Chi-2.

[e]Six-year-old boy.

deposition because of rapid growth, the Pu_{sk} calculated from this sample also exceeded 100%. The measured ash content of the "cortex" sample was 37%, the same as that of the specimen designated as tumor.

The composition of children's bone seems not to have been measured, but the humerus shaft of the newborn rhesus monkey is 49% ash and that of a one-year old monkey is 58% ash (P. W. Durbin, unpublished). Although not stated, the biopsy specimen may have been taken from the lower femoral metaphysis, the site of a pathological fracture 3 months earlier.

The liver of Chi-2 was almost nonfunctional, permitting diversion of a larger than usual fraction of the injected Pu to the skeleton. For this reason Chi-2 should be omitted from any average that purports to describe the deposition of Pu in healthy well-nourished adults. By the same line of reasoning, Pu_{sk} of HP-11, whose liver was only partially functional, should be considered an upper limit for the normal case. If the three obviously unusual cases (HP-12, Chi-2, and Cal-2) are eliminated, the average Pu deposition in the skeletons of seven cases is calculated to be 52% by the material balance method and 49% by the ponderal method, with individual values ranging from 38% to 65%.

PLUTONIUM IN BLOOD AFTER INTRAVENOUS INJECTION

Serial blood samples were drawn at irregular intervals from eleven of the Pu-injected individuals.[19] The first sample was taken 4 hr after injection in all but one case, Chi-1.[18] The longest post-injection time at which a reliable blood sample was obtained was 46 days. A semilogarithmic curve of Pu in the blood was prepared for

each of the ten individuals from whom more than three blood samples were taken.

Because only a few blood samples were drawn at irregular intervals, it was necessary to make some assumptions about the general properties of the individual curves so that all the blood data could be used. Two early blood samples were drawn from Chi-1;[18] whole blood contained 3.2 μg Pu/ml and 2.5 μg Pu/ml, 10 and 45 minutes after injection of Pu(VI) citrate. Using 7.71% of the body weight (the value used for the blood volume by Langham et al.[19]), one calculates the Pu content of the blood at these two times as 29% and 23%, respectively. Some early evidence was obtained from rats,[88] but subsequently not confirmed in the dog,[14,28] that Pu(VI) might leave the circulation faster than Pu(IV). However, these two early measurements in man agree with the observations in both the dog[14,28] and the sheep[39] in that the initial slope of the Pu plasma disappearance curve is quite steep.

For the interval between 4 and 48 hours several of the human Pu blood curves could be superimposed on the dog curve, a portion of which is shown in Fig. 2. In the absence of information to the contrary, it was decided to make the human curves (except for HP-4, whose Pu blood curve appeared not to have any short-lived components) conform to the dog curve during the first 4 hours. All the human Pu blood curves were forced to pass through 66% at 30 minutes, yielding an average initial slope with a half-time of 50 minutes, as shown in Table V.

In some cases one of the two key points, 4 or 24 hours, was missing. The missing values were estimated from the other cases that most closely

Table V. Intercepts and half-times of unanalyzed semilogarithmic curves of Pu in human blood. Pu(IV) citrate injected intravenously.

Case	Day of last sample	PA_1 (%)	PS_1 (min)	PA_2 (%)	PS_2 (hr)	PA_3 (%)	PS_3 (days)	PA_4 (%)	PS_4 (days)	PA_5 (%)	PS_5 (days)	Circulation status[a]
HP-1	10	100[b]	50[b]	53	18	30	2.0					
2	22	100[b]	50[b]	55	16	26	1.6	5.6	7.4			Cardiac failure[c]
3	23	100[b]	50[b]	32	22.7	22	1.8	3.5	6.0			Edema[d]
4	23	-	-	100	18.5	44	2.2	13.0	5.5			Hypertension[e]
5	23	100[b]	50[b]	43	8.5	15	0.8	1.1	6.5			
6	22	100[b]	50[b]	46	11.5	21.5	1.0	2.4	4.5	0.29	95	
7	29	100[b]	50[b]	37	20	24	2.0	3.6	6.0	0.48		Cardiac failure[f]
8	42	100[b]	50[b]	45	14.5	22	1.7	4.3	6.0	0.24		
9	36	100[b]	50[b]	51	12	16	2.6	6.9	6.6	0.58		
10	30	100[b]	50[b]	60	18.5	33	2.3	4.8	6.8	0.49		Cardiac failure[g]
12	46	100[b]	50[b]							0.64	82	
Normal circulation,		No. cases		5	5	5	5	5	5	4	2	
Mean				47.6	12.9	20.9	1.62	3.7	5.9	0.44	88	
±S.D.				4.2	3.6	6.0	0.74	2.5	1.5	0.20	13	
Impaired circulation,		No. cases		5	5	5	5	4	4	2		
Mean				56.8	19.1	29.8	1.98	6.1	6.3	0.48		
±S.D.				26.9	2.5	9.0	0.29	4.0	0.8	0.01		

[a]Status of circulation obtained from case histories (below).

[b]Fitted to 100% at t = 0, and to 66% at t = 30 min.

[c]HP-2: "Essential hypertension with hypertensive cardiovascular disease and coronary insufficiency."

[d]HP-3: "Hepatitis with hyproproteinemia and dependent edema."

[e]HP-4: "Cushing's syndrome with hypertension, hypertensive heart disease."

[f]HP-7: "Rheumatic heart with mitral insufficiency and auricular fibrillation, hospitalized for cardiac decompensation."

[g]HP-10: "Acute congestive heart failure."

resembled the defined portions of the incomplete curves. Blood samples were taken from four cases--HP-6, HP-8, HP-9, and HP-12--at long enough times after the Pu injection to demonstrate a leveling-off trend; in two other cases--HP-7 and HP-10--the intercept of a slower component could be estimated. The intercepts and the half-times of the unanalyzed Pu blood curves are shown in Table V. In this and subsequent discussions of data presented as semilogarithmic plots, the slopes of the segments of the experimental curves are presented in terms of their half-times: half-time = $0.693/\lambda$, where λ is the slope in units of time^{-1}. Half-times of raw curves are designated as S, and half-times of the exponential equations of these curves are designated as T. Intercepts of raw curves are designated as A, and the coefficients of the exponential equations as α. Individual Pu blood curves are shown in Fig. 2 along with the curves for dog and sheep.* Case HP-2 is shown as typical of the curves of most of the cases. Case HP-4 was the most unusual--rapid components were missing, and Pu remained in the blood for a much longer time than in the other areas. The blood curve of case HP-7 is shown to demonstrate the leveling trend after the fifteenth day.

The remarkable finding is the similarity of the half-times of the individual Pu blood curves. In spite of the variety of their illnesses, the Pu kinetics of these individuals revealed a common pattern. Comparison with the animal curves, Fig. 2 and Table VI, revealed an equally

*The Pu blood curve for the dog was constructed from the data given in Figs. 1 and 2 of Stover et al.[28] % Pu per ml plasma was converted to % Pu in the total blood volume by using the blood volume determined for the beagle.[67] Long-term data were obtained from Table I in Stover et al.[29] Data for the sheep were read from Fig. 3 of McClellan et al.[39]

remarkable similarity among the different species, an observation that has also been commented upon by Turner and Taylor.[89] As it moves out of the circulation, Pu is evidently tracing some fundamental process common to all these species, and one that is only minimally disturbed by the specific pathological conditions of these human cases.

Although similar to one another, the individual intercepts and half-times of the components designated P_2, P_3, and P_4 were not normally distributed about their mean values. Therefore, it was necessary to seek some aspect of the chemical status of Pu or the physiological status of the patients (or both) that would account for the variations of the coefficients and half-times.

Binding and transport of iron

Pu(IV) has been shown to combine with proteins in the plasma of the rat,[30,89] dog,[32,33] and man[31]--in particular the iron-transport protein, transferrin. The properties of transferrin and its metabolism, and the transport of iron and the release of iron into developing red cells have all been covered in an excellent new review by Katz.[35] Release of iron from transferrin is a closely controlled process that proceeds rapidly; the plasma clearance of ^{59}Fe after injection of pre-equilibrated ^{59}Fe-transferrin has an average half-time of 96 min.[34,35] Once it is bound to transferrin, Pu(IV) appears to be released more slowly, and the mechanism of release remains to be elucidated. However, because such a large fraction of Pu(IV) introduced into the circulation in monomeric form is quickly bound to transferrin--85% in 1 hour in the rat[89] and 96% by the seventh hour in the dog[33]--the working hypothesis was adopted

that Pu bound to transferrin traces, at least in part, the metabolism of the carrier protein.

The rates of production and destruction of transferrin (hence, the amount of transferrin circulating[35]) and the latent binding capacity (binding sites not already occupied by iron) are closely controlled and are related to hematopoiesis and dietary iron intake.[36] For example, both the amount and latent binding capacity of transferrin are increased following acute hemorrhage and in iron-deficient anemia, and both are reduced in hemolytic anemias, acute hepatitis, and hemochromatosis.[36] The extent of Pu-transferrin binding and the rate of its release would appear to be related to and affected by the status of hematopoiesis.

That some of the Pu not promptly bound to protein moves into the extracellular fluid can be inferred from the rapidity with which Pu initially leaves the circulation, but without appearing in significant amounts[63] in the excreta or the major organs of deposition. Nearly half the body transferrin and the iron bound to it are extravascular.[35] The slow return of Pu to the circulation and its nearly complete protein binding after the first hour strongly suggest that some Pu escaping into the extracellular fluid returns in bound form. The rates of movement of (a) unbound Pu out of the circulation and into the extracellular fluid, (b) Pu returning to the circulation bound to transferrin, and (c) Pu-transferrin into extracellular fluid[35] and excreta[35,90] should all be influenced by the efficiency of the circulation.

Effect of circulatory impairment on disappearance of Pu from blood

Individual histories revealed that four persons--HP-2, HP-4, HP-7, and HP-10--were suffering from various heart and circulatory ailments,

all of which are associated with increased tissue lymph retention and decreased venous return. HP-3 was edematous as a result of hepatitis and accompanying pruritic dermatitis, and her rate of tissue fluid movement was probably depressed. The parameters of the blood Pu curves of these five cases were compared with those of the remaining five cases, whose cardiovascular systems were apparently normal for their ages. The blood volumes of those patients with circulatory impairments lost Pu more slowly; the half-times of P_2 [PS_2 (normal) = 12.9 ± 3.6 hour, and PS_2 (impaired) = 19.1 ± 2.5 hour] were significantly different ($P = 0.01$).[91] Although they could not be examined, the earliest components (combined here as P_1) were probably also slowed by circulatory impairment. Half-time PS_3 was slower in the persons with poor circulation, but the difference was not significant. No effect of circulatory impairment was detected on component P_4, suggesting that this and later components are only minimally influenced by circulatory status. The intercepts PA_2, PA_3, and PA_4 were higher when the circulation was not normal, but the scatter was so great that these differences were not significant. The amount of Pu circulating is also influenced by the extent of transferrin binding (related to erythropoietic status), but the sample size was too small to permit multivariate analysis.

Construction of a Pu blood curve

A five component exponential Pu blood curve was constructed by use of the mean intercepts and half-times of those individuals who were judged to be free of debilitating heart or vascular disease. Each mean component was plotted as a straight-line segment, and the equation of the composite curve was obtained by standard graphic methods. The parameters

of the equation of the human blood curve are given in Table VI along with those of the Pu plasma or blood curves of several other species.

The physiological processes associated with various segments of the Pu plasma curve have not yet been identified. Examination of the similarities and differences among the individual human plasma curves and between the different species suggest the following possibilities.

Only components P_1 and P_2 were affected by impairment of the circulation. Component P_1 (not well defined for man, half-times ranging from a few minutes to about 1 hour) seems to be associated with circulatory mixing, movement of unbound Pu into extracellular fluid, and uptake of unbound Pu in bone and liver. Component P_2 (half-time 7 to 8 hours, somewhat shorter in the sheep) seems to be related to the accumulation of bound Pu by bone and liver.

Iron metabolism suggests the mechanisms leading to components P_3 and P_4. Component P_3 (half-time 1 to 2 days and not observed in the rat) may be related to the return of Pu-transferrin from extracellular fluid to the circulation. The last short-term component, P_4 (half-time 5 to 6 days) may be related to the destruction of the protein portion of the Pu-transferrin complex, or to a slower component of feedback from soft tissue.

Studies of the material balance of Pu in swine suggest loss of Pu from bone as an important source of plasma Pu after the first few post-injection days. A long-term component, P_5, was found for the dog and pig (half-time about 230 days), and is probably related to feedback of Pu from short-lived bony structures and from soft tissues. Only the

dog has been observed for a long enough time to permit identification of a very slow component (half-time about 5500 days), which may be related to release of Pu from the liver as well as from slowly metabolizing portions of the skeleton.

RENAL EXCRETION OF PLUTONIUM

The daily urinary excretion of each Pu-injected individual was given in Table 6 of Langham et al.[19] through the end of excretion collection or through 138 days after Pu injection. Additional excretion data for Chi-1, Chi-3, and Cal-1 through 155, 163, and 341 days, respectively, were available in the original references.[47,53,57] The data for each individual were plotted both as power functions and exponential functions of time. No individual's data could be fitted well to a single power function over the entire interval of excretion collection, and in only a few instances could the urine data be fitted by two power functions.* As Snyder[24] has pointed out, there is a great deal of scatter in the individual data; it could be caused by incomplete collection, analytical errors, or fluctuations in the physical condition of the patients. Cal-1 underwent a total gastrectomy 4 days after the Pu injection, and was fed intravenously for several days thereafter, to mention only one example. Nevertheless, with a little imagination and courage, straight-line segments could be drawn on the semilogarithmic plots of daily urinary

*It seems that the good logarithmic fit of these same data obtained by Langham et al.[19] was due at least in part to (a) neglecting the first 10 days, (b) using the average daily urine output for the group without regard for their medical status, and (c) skewing of daily averages towards low values after the first 30 days; most of the later urine samples were obtained from those individuals who consistently excreted the lowest amounts of Pu.

excretion, and the resulting curves analyzed graphically. The individual urine curves are shown in Appendix 9.

Urinary excretion of iron

Because such a large fraction of the circulating Pu is bound to transferrin,[33] it is appropriate at this point to summarize what is known or can be inferred about the renal excretion of iron, the metal normally transported by transferrin. The transferrin-iron binding constant is estimated to be of the order of 10^{36}, greater than that of any known natural or synthetic chelate.[35] Under normal physiological conditions only a tiny fraction of plasma iron exists in forms other than bound to transferrin. A small fraction circulates as hemoglobin bound to haptoglobin.[92] Chelates of iron with lower-molecular-weight compounds may exist, but have not been identified. Urinary excretion of iron is low, only 0.1 mg to 0.2 mg daily, and amounts to a urinary clearance of about 3% of plasma iron daily,[93] except in hematuria (renal bleeding), hemoglobinuria (aberrant red cell destruction), and hemosiderinuria (iron overload and some hemolytic anemias associated with excretion of hemosiderin granules).[36] The normal mechanisms of urinary iron excretion probably include (a) filtration of low-molecular-weight chelates, (b) exfoliation of kidney, bladder, or urethra cells, all of which contain small amounts of iron, and (c) leakage of transferrin-bound iron through the glomerulus or tubules. Another possible source of urinary iron may arise during transferrin catabolism in the kidney, but the mechanism by which some of the liberated iron might pass into the urine is obscure. Filtration of low-molecular-weight iron chelates would not appear to be an important normal source of

Table VI. Disappearance from circulating blood of intravenously injected Pu(IV) citrate. Parameters of equations[a] of experimental plasma (or whole blood)Pu curves of rat, dog, and sheep; and of constructed blood Pu curve for a human being with no circulation impairment.[b]

Species	Day of last sample	Pα 1 (%)	PT 1 (min.)	Pα 2 (%)	PT 2 (hr)	Pα 3 (%)	PT 3 (days)	Pα 4 (%)	PT 4 (days)	Pα 5 (%)	PT (days)	Reference
Rat	8	60.3	58	37.3	8.2			0.8	6.0			89
Dog[c]	5	45	3-111	20.5	7.8	44	1.7					14
Dog	3,000	44	11-48	19.5	7.3	30	1.0	2.1	5.0	0.081	220[d]	28,29
Sheep	10	68	24	25	2-5	5.8	1.6	1.1	4.9			39
Pig	475									0.50	230[e]	40
Man[a]	42	52.4	20	27.1	7.3	17.2	1.2	3.3	5.0	0.44	88	

a $P_t(\%/day) = \Sigma_{n=i}^{\eta} P\alpha_i \exp(-0.693t/p\tau_i)$.

b See text and Table V.

c Pu(VI) citrate, 0.05 μCi/kg.

d An additional long-term component emerged at 800 days postinjection. $P\alpha_6 = 0.045\%$, $PT_6 = 5500$ days[29]

e Average of two components: $P\alpha_5 = 0.41\%$, $PT_5 = 66$ d; $P\alpha_6 = 0.33\%$, $PT_6 = 380$ d.

urinary iron, but the ability of the kidney to excrete unbound iron can be inferred from the observation by Dubach et al.[94] that 1% to 2% of injected ^{59}Fe could be found in the first urine samples when the radioactive tracer was given as complex ^{59}Fe ascorbate.

Because urine is a plasma filtrate, the rate of Pu excretion in urine will early reflect by analogy with iron such processes as the rates of circulation and tissue deposition, and later the rates of tissue feedback. The amount of Pu excreted in the urine at any time will depend at least in part upon the extent of Pu-transferrin binding (or binding to other proteins) and the filterability of low-molecular-weight Pu chelates.

Effect of renal and hematopoietic function on Pu excretion

Examination of the original tabulation of the urine data[19] suggested that some individuals consistently excreted more Pu than others. In order to discover whether urinary Pu excretion could be related to physiological status, urinary Pu was summed for the earliest and latest 6-day intervals in which excreta were collected from all the patients, 1 through 6 days and 19 through 24 days, as shown in Table VII. Excreta were summed over intervals to reduce the influences of daily fluctuations, poor sampling, and missing samples. Missing values were interpolated from the individual urine Pu curves in Appendix 9.

Each medical history was examined for information on renal function, hepatic protein synthetic capacity, and hematologic status. Hematological examinations were reported for 12 cases (9 of those given Pu(IV) citrate) close to the time of their Pu injections. The pertinent data are included in Appendix 2. Four patients--HP-1, HP-7, HP-9 and HP-12--could

Table VII. Influence of anemia and impaired kidney function on early urinary Pu excretion in man.

Case	Red cell count	Kidney function	% Pu in urine 1-6 days	% Pu in urine 19-24 days
Pu(IV) citrate				
HP-1	Low	N[a]	0.670	0.121
HP-2	N	N	1.240	0.104
HP-3	N	N	1.198	0.091
HP-4	N	Ab[b]	1.264	0.147
HP-5	N	N	0.641	0.117
HP-6	N	N	0.914	0.080
HP-7	Low	N	0.790	0.057
HP-8	N	N	1.038	0.159
HP-9	Low	N	0.479	0.186
HP-10	N	N	1.281	0.108
HP-12	Low	N	0.482	0.173
Pu(VI) citrate or nitrate				
Chi-1	Low	Ab	3.072	0.161
Chi-2	Low	Ab	0.503	-
Chi-3	?	?	1.231	0.094
Cal-1	Low	N	0.855	0.035
Pu(IV) citrate, only				
Erythropoietic status			Mean ± S.D.	Mean ± S.D.
Anemic, No. cases	4		0.605 0.152	0.134 0.058
Normal, No. cases	6		1.052 0.236	0.110 0.027
"p"[d]			<0.01	>0.5

[a] N = normal.

[b] Ab = Abnormal, not included in calculated means.

[c] Urine and feces combined.

[d] T-test of Fisher.[91]

definitely be described as anemic. HP-4 was judged to have abnormal kidneys. HP-2, HP-5, HP-6, HP-8, and HP-10 were judged, on the basis of available information, to have no obvious impairment of renal, hepatic, or bone-marrow function. HP-3 was also included among the normals, because by the time of the Pu injection she had a nearly normal hemogram. Chi-1, Chi-2, and Cal-1 (who received Pu(VI)) as citrate or nitrate) were all anemic, and two had impaired kidney function. There is no published information about the physiological status of Chi-3, who had an advanced case of Hodgkin's disease.

In three cases renal function was considered to be abnormal. HP-4 was suffering from chronic nephritis and ultimately died of uremia. Her hemogram suggested a lower-than-normal iron-binding capacity, but her Pu excretion was not excessive, as might have been expected had her kidneys been leaking protein. The other cases with renal impairment were given Pu(VI) citrate. There are no plasma curves for these cases, and little is known about the possibility that Pu(VI) citrate may be filtered by the kidney with greater efficiency in the first few minutes after injection and before protein binding occurs. Chi-1 was suffering from mild chronic pyelonephritis, but was also anemic. His very high early Pu excretion is puzzling. Apparently Chi-2 had little remaining functional kidney tissue, but she also was very anemic. Her low initial Pu excretion could be the result of impaired renal filtration or elevated transferrin binding or both. There is no published information about either the functional status of kidney or marrow of Chi-3. He was suffering from Hodgkin's disease at the time of the Pu injection, and died about 5 months afterward. His slightly elevated urinary Pu during

the first 6 days after injection suggests that his transferrin binding capacity was probably within normal limits. Except after acute hemorrhage, patients suffering from Hodgkin's disease often have a hemolytic anemia which is associated with a reduced transferrin saturation. It would appear that the effects of most common renal disturbances--whether caused by infections, hypertension, or malignant invasion--are to increase protein excretion and reduce reabsorption of cations. Both processes would contribute to an elevated urinary Pu excretion.

The influence on urinary Pu excretion of anemia associated with an elevated latent iron binding capacity (reduced transferrin saturation) is clearer. During the first 6 days p.i. the four anemic Pu(IV)-injected patients excreted significantly less Pu in their urine than did those whose hemograms were presumably normal. Lower initial Pu excretion is what whould be expected on the basis of the increased binding capacity of transferrin associated with most anemias.[36] During the interval of 19 to 24 days, the last 6 days for which excreta were collected from all the Pu(IV)-injected patients, the urinary Pu of the anemic patients was slightly more than that of the hematologically normal patients though not significantly so.

Construction of a urinary Pu excretion curve

Plots of urinary Pu data were prepared and handled in the same way as the Pu blood curves discussed in the preceding section. Straight-line segments were fitted by eye to the data points on the semilogarithmic plots collected in Appendix 9. The intercept and half-time of each curve segment determined for each individual are shown in Table VIII. The urine curves of the four persons studied longest (HP-12, Cal-1, Chi-1, and Chi-3) and the best curves that could be drawn from data for the dog and

Table VIII. Intercepts and Half-Times of the Unanalyzed Human Urine Pu Curves.

Case	Day of last sample	UA_1 %/day	US_1 days	UA_2 %/day	US_2 days	UA_3 %/day	US_3 days	UA_4 %/day	US_4 days	UA_5 %/day	US_5 days
Pu(IV) citrate											
Normal											
HP-2	34	0.58	1.9	0.105	8.	0.0098[b]					
HP-3[d]	23(1,610)[c]	0.76	1.1	0.270	2.8	0.0205[b]		0.0035[b]		0.0011[b]	
HP-5[d]	22	0.40	1.1	0.050	9.3	0.0240	71				
HP-6[d]	22(1,698)[c]	0.35	2.1	0.092	6.5	0.017[b]		0.0050[b]		0.0015[b]	1,250[b]
HP-8	65	0.46	1.25	0.148	5.1	0.023	64				
HP-10	30	0.55	1.9	0.162	5.						
Anemic											
HP-1	25	0.21	2.7	0.097	9.						
HP-7	37	0.28	2.6	0.044	9.	0.0100[b]					
HP-9	36	0.24	1.2	0.100	5.2	0.0400	45				
HP-12	58		-	0.112	7.	0.0330	42				
Abnormal kidney											
HP-4	26	0.50	1.9	0.200	7.						
Pu(VI) citrate or $PuO_2(NO_3)_2$											
Anemic											
Cal-1	341	0.60	1.0	0.180	4.6	0.012	71	0.0019	460		
Chi-1[e]	155	2.53	0.33	0.220	3.6	0.035	67				
Chi-2[e]	15	0.27	1.4	0.058	8.0						
No information[f]											
Chi-3	164	1.50	0.7	0.038	9	0.020	42	0.011	440		

[a]Renal function and erythropoiesis judged to be within normal limits.

[b]Estimated from constructed curves shown in Appendix 9. US_5 of case HP-6 defined by two points at 525 and 1,610 days.

[c]Single sample taken at these late post-injection intervals.

[d]No published hematologic data, but presumed to be within normal limits.

[e]Kidneys abnormal.

[f]Both renal and hematopoietic function can be impaired in the advanced stages of Hodgkin's disease.

the pig are compared in Fig. 3. The majority of the individual Pu urine curves contained two to four distinct segments, depending upon how long excreta were collected. Portions of three urine curves (HP-7, HP-8, and Chi-1) could have been resolved into several segments with only slightly differing slopes. In these instances the best single line was drawn through the portion in question, and although this average slope did not fit the data points so well it did permit the estimated parameters of these curves to be included in the means for the entire group of patients.

The means ± S.D. of the raw intercepts and half-times were calculated (see Table 9) for the six Pu(IV)-injected persons judged to have normal kidney and hematopoietic function and for the four Pu(IV)-injected persons judged to be anemic. The intercepts of the first two components, UA_1 and UA_2, of the Pu urine curves of the presumably normal persons were almost twice as large as UA_1 and UA_2 determined for the anemic cases. The intercept, UA_3, of the normal group was substantially lower than UA_3 of the anemic group. The half-times of these three components of the Pu urine curves were not affected by anemia or kidney disease. Although the amounts of Pu excreted in the urine were altered as a result of the various physiological processes associated with anemia, the rates of these processes were apparently unaffected.

The average intercept, UA_1, of the Pu(VI)-injected cases was greater, and the half-time, US_1, was less than the values of these parameters determined for either the normal or anemic Pu(IV)-injected group. The S.D.'s of the Pu(VI) parameters are large, reflecting the variable physiological status of the individuals. If Chi-2 is omitted

(she had little functional kidney tissue or bone marrow remaining), the average amount of Pu(VI) at UA_1 is even greater, and the half-time of the initial elimination, US_1, is even shorter. The greater early urinary excretion of Pu(VI) suggests that Pu in this form, in particular Pu(VI) citrate, is more easily filtered by the kidney after injection than is Pu(IV) citrate. The more rapid decay of the initial urinary component is in accord with Bruenger's suggestion[95] that Pu(VI) protein binding is more stable than that of Pu(IV).

The average intercepts and half-times of the slower components, U_2, U_3, and U_4, of the Pu(VI)-injected persons were either the same as or not very different from the values of these parameters determined for the group of Pu(IV)-injected cases with normal kidneys and normal hematopoiesis.

For radiological protection purposes the need is characterization of a Pu urine curve representative of an adult human being in reasonably good health. Previous participants in this exercise have worked with mean daily urinary Pu values without regard to the health status of the individuals contributing data to each mean or to the fluctuating sample size of each mean.[19,24,25] An attempt has been made in this analysis to exclude data from those persons judged to have obviously abnormal kidney function or abnormal plasma Pu binding (the anemic persons), and to avoid giving undue weight to data from an individual or a small group. A five-component exponential curve was constructed; the raw intercepts and half-times are shown in Table IX, and the parameters of its equation appear in Table X. The early portions of the

Table IX. Comparison of the Half-Times and Intercepts of Unanalyzed Urine Curves of Pu(IV)Citrate-Injected "Normal"[a] and Anemic Cases and of Pu(VI)-Injected Cases, and the Best Estimate of the Half-Times and Intercepts of the Pu Urine Curve of a Normal Adult Human Being.[a]

Pu(IV)citrate	UA_1 %/day	US_1 days	UA_2 %/day	US_2 days	UA_3 %/day	US_3 days	UA_4 %/day	US_4 days	UA_5 %/day	US_5 days	Day of last sample
Normal[a], No. cases	6	6	6	6	5	2	2	-	2	-	1,645
Mean	0.54[b]	1.65	0.138	6.1	0.0189	68	0.00425		0.0013		
± S.D.	0.12	0.44	0.05	2.3	0.006	7	0.0015		0.0004		
Anemic, No. cases	3	3	4	4	3	2	-	-	-	-	58
Mean	0.24	2.1	0.088	7.6	0.0277	44					
± S.D.	0.03	0.58	0.03	1.6	0.005	3					
Pu(VI)[c], No. cases	4	4	4	4	3	3	2	2			341
Mean	1.22	0.86	0.124	6.3	0.0223	60	0.00645	450			—
± S.D.	1.01	0.45	0.089	2.6	0.012	16	0.0091	20			
Normal man[a,d]											
Pu(IV)citrate, No. cases	6	9	6	10	5	4	2	0	2		
Pu(VI), No. cases	0	0	0	4	0	3	0	2	0		
Mean	0.54	1.8	0.138	6.4	0.0189	57	0.00425	450	0.0013	4,000	
± S.D.	0.12	0.56	0.05	2.1	0.006	14	0.0015	20	0.0004		

[a]Renal function and hematopoiesis judged to be within normal limits.

[b]Underlined means were compared with the means immediately below by use of the t-test and "P" = 0.05[91].

[c]Three Pu(VI) cases were known to be anemic. The hematologic status of Chi-3 was not known.

[d]Selection of parameters of human Pu urine curve described in text.

Table X. Urinary excretion of Pu by an adult man, young adult beagle, and adolescent miniature pig. Parameters of exponential equations of urine curves.[a]

	$U\alpha_1$	UT_1	$U\alpha_2$	UT_2	$U\alpha_3$	UT_3	$U\alpha_4$	UT_4	$U\alpha_5$	UT_5
	%/day	days	%/day	days	%/day	days	%/day	days	%/day	days
Normal man[b]	0.41	1.23	0.12	5.5	0.013	42	0.003	300	(0.0012)	(4,000)
Dog[c]	4.6[d]	0.48[d]	0.15	3.3			0.008	450	0.004	3,850
Pig[e]	0.48	0.6	0.23	2.5	0.05	10	0.042	380		

[a] $U_t(\%/day) = \Sigma_{n=i}^{n} U\alpha_i \exp(-0.693t/UT_i)$.

[b] Kidney function and hematopoiesis presumed to be within normal limits.

[c] Stover *et al.*[29] and B. J. Stover and D. R. Atherton, original data; 0.1 μCi/kg and 0.3 μCi/kg groups only.

[d] Average of two components, $U\alpha_{1a}$ = 4.1%/day, UT_{1a} = 0.2 day; $U\alpha_{1b}$ = 1.9%/day, UT_{1b} = 0.8 day.

[e] Data read from Fig. 1 of Clarke *et al.*[40]

curve were pieced together from the half-times and intercepts defined by the continuous collection of excreta from the Pu-injected individuals. The later portions of the curve, after 350 days, were estimated from three late urine samplings obtained from two Pu-injected persons and from animal data.

Evaluation of half-times

The half-times of the early components of the Pu urine curve were not noticeably affected by the physical disabilities of the individual Pu(IV)-injected patients, and all the half-time determinations derived from their Pu urine curves were included in the calculated average half-times for each component. Pu(IV) is deemed most likely to be the chemical form of Pu encountered in an occupational exposure, and for this reason the values obtained for US_1 in the Pu(VI)-injected cases were omitted from the calculated means. The half-times determined for the later components of the urine curves of the Pu(VI)-injected individuals were not different from those determined for the persons given Pu(IV); therefore, all available half-time determinations have been included in calculation of the half-times, US_2, and US_3. Only Chi-3 and Cal-1, who were both injected with Pu(VI), provide any estimate of the half-time of the fourth component, US_4, and it should be emphasized that neither was followed long enough to define US_4 closely.

The only human Pu urine data after postinjection intervals sufficiently long to permit estimation of the slope of the next slow component, US_5, are two samples obtained from HP-6, 525 and 1610 days p.i. The line joining these two points has a half-time of 1250 days, only one-third the value of the comparable component of the Pu urine curve of the dog (see

Table X). The half-times of the components US_3 and US_4 are not defined for HP-6 because continuous collections were terminated too soon. The half-times of the two earliest components, US_1 and US_2, for HP-6 are the same as those of the other cases, and there is no reason to suspect that US_3 and US_4 for HP-6 would be different from those of the other patients. If US_3 and US_4 are similar to the other cases, then the urine curve for HP-6 should bend between the two late sample points, and the half-time of the slowest component should be greater than 1250 days.

Some long-term urine data from two occupationally exposed persons are shown in Fig. 4: WBG, DLW, and WAB[19], from whom urine specimens were obtained periodically up to 1698 days after termination of Pu exposure; and LASL-1 (described by Foreman et al.[58]), who was followed for 3500 days after cessation of his initial high-level Pu exposure. The latter case is complicated because the individual returned to work with Pu, but at much lower levels than previously, 2350 days after the end of his first Pu exposure period. The occupational data suggest that the longest half-time of the human Pu urine curve is more than 1250 days, and perhaps as long as 13,400 days--the least-squares-fitted slope of the LASL-1 urinalysis data.* However, the Pu excretion of LASL-1 cannot be considered definitive, because after day 2350 his urinary Pu may have been augmented by re-exposure to small amounts of Pu. In the absence of reliable human data, and because the half-times of comparable early

*The data points shown in Fig. 4 for case LASL-1 are averages of all the urinalyses taken during each 6-month interval: the original data appear in Table III of Foreman et al.[58] These averages were not weighted for the number of analyses, and zero values were ignored.

portions of the human Pu urine curves are similar to those in the large species studied (dog and pig), 4000 days (11 yr) was selected as a working value for US_5 for man. It is likely that US_5 is longer than 4000 days, or that there is a slower sixth component (approaching a constant level of Pu excretion). The source of Pu in the urine after long postinjection intervals is feedback of Pu released from tissue and bone turnover, and the rates of some of these processes may well be longer in man, the longest-lived of the three species.

Lagerquist et al.[96] reported an accident involving contamination of a Pu worker designated RF-2075 (S. E. Hammond, private communication). He inhaled some Pu, and his body surface was contaminated, but the bulk of his internal burden was apparently the result of Pu embedded in an injured hand. Twelve days after the accident 134 μCi (98%) of the total of 136 μCi of Pu in his hand was removed surgically, and his urinary Pu level dropped to one-third of the preoperative level. This observation suggests that a large fraction of his systemic Pu burden had been acquired (whether by absorption from the injured hand, inhalation, or through contaminated skin) very shortly after the accident and that he could be considered to have had a single acute exposure. Two later operations removed all but 0.6 μCi of the Pu in his hand. DTPA treatments, which had been given almost continuously, were stopped for a time after both later operations, obscuring any further postsurgical drops in urine Pu level.

The urinary Pu excretion of RF-2075 is plotted semilogarithmically in Fig. 5 from data read off the curves published by Lagerquist et al.[96] This is admittedly a complicated case; it should be emphasized the indi-

vidual was treated almost continuously with DTPA, and three operations were performed to remove the Pu from his hand. Fig. 5 shows, however, that the raw half-times of his Pu urine curve are remarkably close to those obtained from the urine curves of the Pu-injected persons (see Table IX). On the other hand, the intercepts of the Pu urine curves of RF-2075 and the Pu-injected cases are quite different, reflecting the changes in Pu deposition pattern brought about by prolonged DTPA treatment. RF-2075 was 48 years old, weighed 81.7 kg, and was in good health at the time of the accident (S. E. Hammond, private communication.) The similarity of the half-times of his urine curve and those of the Pu-injected cases, none of whom could be considered to be in good health, supports the general applicability of the "normal" human Pu curve derived in this paper. In addition, this case supports the view that the amounts of Pu entrained in various physiological processes may be altered, by illness or (in RF-2075) by prolonged DTPA chelation therapy, but the rates of the processes remain essentially constant.

Evaluation of coefficients

The amounts of Pu excreted in the first two urinary phases, represented by the intercepts UA_1 and UA_2, were found to be depressed in anemic persons (presumably because of their elevated iron-binding capacity) and to be elevated when Pu was given as Pu(VI) citrate (presumably because of the more efficient renal filtration of this form of Pu). Therefore, the values selected for UA_1 and UA_2 in the human urinary curve were those determined for the Pu(IV)-injected persons with presumably normal kidneys and hematopoiesis.

The intercepts of the curves obtained from the Pu(VI)-injected series were rejected throughout. Each of the four persons in the series met one or more of the criteria for altered urinary Pu excretion. One, Cal-1, was anemic. Two, Chi-1 and Chi-2, not only were anemic but also had abnormal kidney function. Chi-3 may have had impaired hematopoiesis and renal function at the time of injection, and according to descriptions of the course of Hodgkin's disease, his renal function was almost certainly not normal towards the end of his continuous excreta collections, when he was near death. After the first day the average intercepts of these cases were close to those of the normal Pu(IV)-injected group, but the variation among the individuals was great. After the first few days Cal-1 consistently excreted the least Pu. Urinary Pu excretion of Chi-1 and Chi-3 was consistently in the upper one-third of all the cases.

No Pu(IV)-injected individual provided urine data after 65 days p.i.; however, a third component, U_3, emerged early enough in the cruves of Hp-5, HP-8, HP-9, and HP-12 to identify both an intercept, UA_3, and a half-time, US_3. The last few points on the curves of HP-2, HP-3, HP-6, and HP-7 suggested an inflection and permitted estimation of the intercept of the next component, UA_3. Although they were not included, the values of UA_3 determined for Chi-1, Chi-3, and Cal-1 substantiated the estimates of the mean (UA_3), obtained from the Pu(IV)-injected cases.

Only Cal-1 was followed long enough to identify either an intercept or a half-time of the next component, U_4. Comparison of his daily urinary Pu, 0.0011 %/day between 300 and 350 days p.i., with the urinary Pu of HP-6, 0.002 %/day at 525 days and 0.0011 %/day at 1610 days p.i., suggests

that the value of UA_4 obtained from Cal-1* is probably too low by at least a factor of two. Consequently, the graphic construction method shown in Appendix 9 for HP-6 was used to estimate UA_4 and UA_5 from HP-3 and HP-6. A straight line is defined by the slope and one point. Assuming that the urine samples obtained from HP-3 and HP-6, 0.0008 %/day at 1645 days and 0.0011 %/day at 1610 days p.i., respectively, lay on parallel straight lines with a half-time of 4000 days (the value selected for the half-time, US_5), extrapolation of these lines yields estimates for UA_5 of 0.0011 %/day for HP-3 and 0.0015 %/day for HP-6. By the same reasoning, if the urine sample obtained from HP-6 at 525 days p.i. is on a straight line with a half-time of 460 days (the value selected for US_4), extrapolation yields an estimate of the intercept, UA_4, of 0.005 %/day for HP-6. If the urinary excretion of Pu by HP-3 were the same with respect to that of HP-6 at 525 days as it was between 1610 and 1645 days when both were sampled, then extrapolation of the 460-day line through the calculated point

HP-3 Pu = (0.002 x 0.0081)/0.0011 = 0.0015 %/day at 525 days,

yields an estimated intercept of UA_4 for HP-3 of 0.0035 %/day. All the extrapolated values are shown in Table IX. The values of UA_4 obtained from HP-3 and HP-6 by the extrapolation method described above are about twice the measured value of UA_4 for Cal-1, in agreement with expectation.

GASTROINTESTINAL EXCRETION OF PLUTONIUM

The original Pu fecal excretion data for Chi-1 and HP-1 through HP-12 are given in Table 9 of Langham et al.[19] Fecal Pu for Cal-1 was read from Fig. 1 of Crowley et al.[57] Urine and feces were not separated for Chi-2, and fecal data were not reported for Chi-3. During the first two weeks after injection some individuals consistently excreted more Pu in their feces than did others. In order to determine whether fecal Pu was related to medical status, fecal Pu was summed for each patient over the first and last 6-day intervals for which fecal collections were obtained from all the patients. The results are shown in Table XI.

Fecal excretion of iron

At this point we need to consider the possible mechanism of Pu elimination by the gastrointestinal tract. As discussed in the two preceding sections, Pu transport in blood and Pu filtration by the kidney are largely determined by the percentage of Pu binding to the iron-transport protein, transferrin. The sparingly small gastrointestinal elimination of Pu by larger animals can also be better understood in light of the stability of the complexes of Fe and Pu with transferrin and the high degree of conservation of iron, the multicharged cation normally carried by transferrin.

Approximately 60% (0.6 mg) of the normal daily iron excretion of 1.0 mg takes place via the gastrointestinal tract.[36, 92, 97] Recent studies by Green et al.[97] indicate that secretion in bile accounts for 0.25 mg (33% of fecal excretion), and loss of iron contained in the 50 to 80 g of intestinal epithelial cells that are desquamated daily accounts for another 0.1 mg (13%). The remaining 40% of gastrointestinal iron excretion may be associated with other digestive secretions (gastric, pancreatic, and intestinal juices).[36,92] *Crosby[91] suggests that the gastrointestinal tract is also an important site of transferrin catabolism.

*Green et al.[97] attributed the remaining portion of gastrointestinal iron excretion to blood loss, but their own failure to detect occult blood in the feces of the same subjects does not support that conclusion.

Table XI. Influence of Restricted Food Intake and Abnormal Digestive Secretion on Gastrointestinal Excretion of Pu in Man.

Pu(IV) citrate	% Injected Pu in feces 1 to 6 days	19 to 24 days
Normal diet		
HP-2	1.408	0.231
HP-4	1.420	0.164
HP-5	1.031	0.111
HP-6	0.886	0.080
HP-9	1.504	0.324
HP-12	1.700	0.264
Mean	1.325 ±0.30[a]	0.196 ±0.08[a]
Restricted diet[b]		
HP-1	0.715	0.094
HP-7	.544	0.064
HP-8	0.894	0.158
HP-10	0.591	0.072
Reduced liver function		
HP-3[c]	0.596	0.066
Mean[d]	0.668 ± 0.14	0.091±0.04
Pu(VI) citrate or nitrate		
Cal-1 (restricted diet)[e]	0.324	0.061
Chi-1 (diet not known)[f]	1.811	0.102

[a]Underlined means were compared with means immediately below by the Fisher t-test.[91] Single underline $P < 0.01$; double underline $P = 0.05$.

[b]HP-1 and HP-8 were being treated for peptic ulcers. Restricted diet is assumed for HP-7 and HP-10 because of their severe heart conditions.

[c]Probably jaundiced. See text.

[d]Includes four restricted-diet cases and HP-3 with subnormal liver function.

[e]Total gastrectomy on day 4. Little fecal output until day 18.

[f]Dietary intake may have been voluntarily reduced following mouth surgery on day 2.

Biliary iron secretion was delayed after injection into normal persons of either ^{59}Fecitrate or ^{59}Fe pre-equilibrated with plasma.[96] It was low during the first 24 hours, rose to a maximum at 3 days, and then dropped to a very low level after the fifth day. Peak total fecal iron excretion was delayed even more, rising from about 0.02% of the dose in the first 24 hours to a peak at 5 days, and then declining to about the 1-day level thereafter. Both loss of iron with desquamated cells (human intestinal epithelium has a life span of about 3.5 days[91]) and biliary secretion of labile hepatic iron (before the iron can react to form less soluble forms of ferritin[36]) would contribute to delayed peak fecal excretion. After gastrointestinal transit time has been accounted for, secretion of iron into digestive fluids other than bile would be expected to parallel the level of circulating labeled iron.

Some iron loss by healthy adults appears to be obligatory. Adequate iron levels are maintained by a combination of conservation and close control of absorption.[91, 92] Neither bodily needs or the amounts of iron stored significantly affect iron excretion. In addition, the amount of iron excreted is so small that changes go almost undetected. Normally, transferrin is only about 30% saturated with iron, and in the presence of this large latent binding capacity the amount of iron in the plasma that is not bound to transferrin is negligible. Pu, on the other hand, does not form so stable a transferrin complex, nor is Pu bound so exclusively and quantitatively to transferrin as is iron. Stevens et al.[33] found that about 5% of circulating Pu was not transferrin bound from 7 hours to 7 days after intravenous injection of Pu(IV) citrate in beagles.

It was suggested that early urinary Pu excretion was related in a roughly reciprocal way to the level of transferrin saturation, insofar as the latent binding capacity of transferrin could be inferred from the brief medical

histories of the Pu-injected individuals. By the same line of reasoning, at least two of the proposed gastrointestinal excretory mechanisms -- biliary and digestive-juice secretion -- might also be expected to be influenced by the degree of transferrin saturation. If dietary intake were low or consisted of soft, bland, nonstimulating foods, the volume of digestive secretions might be lower and fecal Pu consequently reduced.

Effect of hepatic and digestive function on Pu excretion

Gastrointestinal tract and liver function and the amounts and varieties of foods eaten were judged to be within normal limits for HP-2, HP-4, HP-5, HP-6, HP-9 and HP-12. HP-1, HP-8, and Cal-1 were being treated for peptic ulcers and were probably taking frequent small meals of soft bland foods to reduce gastrointestinal stimulation secretion. After a total gastrectomy on the fourth day following his Pu injection, Cal-1 passed no feces until day 8, and none were passed from day 10 through day 17. HP-7 and HP-10 were being treated for severe cardiac conditions, and it is considered likely that they too were taking in less than normal amounts of food and liquids to conserve their cardiac output for vital functions and to suppress water retention. HP-3 was being treated for hepatitis, and although it was not stated in her published case history, the presence of pruritic dermatitis strongly suggests that she was also jaundiced, and that her bile output was less than normal.[98] Chi-1 had a malignancy that arose in the buccal cavity. Local surgery was performed to remove the primary tumor 15 days before and 2 days after his Pu injection. Tables 4 and 5 of Russell and Nickson[47] indicate that his output of fecal matter was normal shortly after injection, but that as his condition deteriorated, the buccal lesion recurred and ulcerated to the bone, apparently making intake of ordinary foods difficult. After the hundredth day his fecal bulk was 88 g/day -- the lower limit of normal.[99]

If only the Pu(IV)-injected cases are considered, the average fecal Pu

of those persons judged to have normal gastrointestinal function and normal dietary intakes was nearly twice that of the persons with gastrointestinal difficulties or restricted dietary intakes. The difference was significant during the first 6 days after injection, but of only borderline significance between 19 and 24 days p.i. There were no discernible correlations between fecal Pu excretion and erythropoietic status.

Construction of a fecal Pu excretion curve

The original data from Langham et al.[19] are plotted on the urine curves in Appendix 9. Analysis of the early portions of most of these curves was not possible, because feces were not analyzed daily but as 2- to 6-day pools. Therefore, a cumulative fecal excretion curve was prepared for each case (plotted as a linear function of time). The derivatives of these curves were determined every day for the first 10 days and every fifth day thereafter for the duration of collections or through the fiftieth day. Pooling of fecal samples or intermittent sampling did not distort the fecal rate curves or inhibit their analysis after the fourth week, although the differentiated cumulative curves (not shown here) were smoother. Fecal lag -- that is, gastrointestinal transit time -- was estimated for each case by extrapolating the earliest defined portion of the cumulative curve to % dose/day = 0. The differentiated cumulative fecal Pu curves were replotted on a semilogarithmic scale (not shown), and the unanalyzed half-times, intercepts (at t = fecal lag), and fecal lag times for each case are collected in Table XII. (See the preceding section, on urinary Pu excretion, for details.) The fecal Pu curves of the three persons who were followed for the longest time after injection (HP-7, Chi-1, and Cal-1), and the best curves that could be drawn for fecal excretion of Pu by the dog and the pig are shown in Fig. 6. Except for Cal-1, who passed very little fecal matter during the first 17 days after

Table XII. Half-times and Intercepts of Unanalyzed Differentiated Cumulative Fecal Pu Curves.

Pu(IV) citrate	Day of last sample	Fecal Lag[b] (days)	FA_1 (%/day)	FS_1 (days)	FA_2 (%/day)	FS_2 (days)	FA_3 (%/day)	FS_3 (days)	FA_4 (%/day)	FS_4 (days)
Normal diet										
HP-2	27	2	0.62	2.5	0.16	10.0				
HP-4	82	1	0.75	3.1	0.35	6.0	0.012			
HP-5	22	1.5	1.50	0.7	0.17	6.7				
HP-6	22	1.5	0.60	1.2	0.067	7.5				
HP-9[c]	35	0.5	0.55	4.0	0.27	8.0				
HP-12[c]	46	1.5	0.60	2.0	0.072	16.0	0.020			
Restricted diet										
HP-1	24	1.0	0.33	2.2	0.049	12.7				
HP-7[c]	85	0.5	0.16	3.8	0.105	6.5	0.013	68		
HP-8	64	1.0	0.52	1.8	0.76	16.0	0.017			
HP-10	30	2.0	0.26	2.7	0.094	6.5				
Reduced liver function										
HP-3	23	2.0	0.24	2.7	0.082	7.7				
Pu(VI) citrate or nitrate										
Restricted diet										
Cal-1[c]	341		undefined		0.18	4.6	0.0034	77	0.0006	650
Diet not known										
Chi-1[c]	138	1.0	1.00	1.3	0.18	7.0	0.008	85	0.0018	

[a] Intercept at t = fecal lag

[b] Fecal lag determined by extrapolation of cumulative fecal curve.

[c] Anemic.

injection, all the fecal Pu curves contained at least two well-defined components during the first 3 to 4 weeks. At least four components could be defined for the case followed longest, Cal-1.

The mean ± S.D. of the unanalyzed half-times and intercepts were calculated (see Table XIII) for the six Pu(IV)-injected individuals that were presumed to have normally functioning gastrointestinal tracts and to be eating ordinary amounts of a mixed hospital diet and for the five Pu(IV)-injected persons judged to be taking in less than normal amounts of food or to be on soft diets (including HP-3, who was judged to have a lower-than-normal bile output). The intercepts of the first two components, FA_1 and FA_2, of the fecal Pu curves of the persons having normal digestive function were almost double those of FA_1 and FA_2 calculated for the persons having reduced gastrointestinal function, but the differences were not statistically significant, because of the wide range of the normal cases. The mean intercepts of the third component, FA_3, were the same for the two cases in each group for which FA_3 could be estimated.

The half-times, FS_1 and FS_2, for the two groups were not different, nor were the S.D.'s of their means. The amount of Pu excreted by the gastrointestinal tract appeared to be lower when gastrointestinal secretion was reduced, but the rates of the underlying processes remained unchanged.

Much less Pu is excreted by the human gastrointestinal tract than by that of either the dog or the rat.[10,14,28] This fact puzzled the three groups of original investigators[29, 47,57] because the inital Pu tracer studies in rats and dogs had indicated that the gastrointestinal tract would be the major excretory route. Complete fecal samples are difficult to obtain and difficult to analyze and it is no wonder that after publication of these human investigations, fecal samples were rarely collected from persons suspected of

Table XIII. Comparison of Half-times and Intercepts of Unanalyzed Differentiated Cumulative Fecal Pu Curves of Pu(IV) Citrate-Injected Normal Cases and Those with Reduced Gastrointestinal Stimulation, and the Best Estimates of the Half-times and Intercepts of the Pu Fecal Excretion Curve of a Normal Adult Human Being.

Pu(IV) citrate	FA_1 (%/day)	FS_1 (days)	FA_2 (%/day)	FS_2 (days)	FA_3 (%/day)	FS_3 (days)	FA_4 (%/day)	FS_4 (days)	FA_5 (%/day)	FS_5 (days)
Normal diet and secretion[b]										
No. cases	6	6	6	6	2					
Mean	0.77	2.3	0.18	9.2	0.016					
± S. D.	0.36	1.2	0.12	3.7						
Restricted diet[c]										
No. cases	5	5	5	5	2	1				
Mean	0.30	2.6	0.081	9.9	0.015	68				
± S. D.	0.13	0.8	0.02	4.3						
Normal man[b]										
No. cases[d]	6	12	6	13	4	3		1		
Mean	0.77	2.3	0.18	8.9	0.016	77	(0.003)[e]	650	(0.0012	4000)[e]
± S. D.	0.36	1.0	0.12	3.7	0.004	9				

[a] Intercept at t = fecal lag

[b] Liver function and gastrointestinal stimulation and secretion judged to be within normal limits.

[c] Includes HP-3, hepatitis.

[d] Mean half-times include Cal-1 and Chi-1

[e] Estimated; see text

having sustained a Pu exposure.

The method used to construct an exponential model of human Pu fecal excretion was the same as described earlier for construction of the urinary Pu curve. There are fewer fecal Pu measurements. No late fecal samples were obtained from any of the Pu(IV)-injected cases. The meager fecal data available from occupationally exposed persons are complicated either by some inhalation exposure or by chelate therapy, or both.[96, 100] Therefore, all the long-term estimates rest on the two cases that were followed longest, Chi-1 and Cal-1, neither of whom had normal gastrointestinal function during the late collection periods. The long-term data from the dog and pig were useful in predicting long-term trends.

Evaluation of half times

The raw half-times of the first two components of the normal Pu fecal curve (Table XIII) are the averages of FS_1 and FS_2 determined for all the cases. All cases were included, because neither the medical status of the individuals nor the chemical form of Pu administered appeared to change the rates of the processes leading to these fecal-curve components. Therefore, FS_1 and FS_2 are well defined, and each is the mean of 12 to 13 separate determinations. The variability is great, however, and the S.D.'s of these half-times are about 50%.

FS_3 could be determined only for HP-7, Chi-1, and Cal-1. There was good aggreement among the three values, and all were used to calculate FS_3 shown in Table XIII. A fourth component, F_4, was observed only for Cal-1. FS_4 emerged in the Cal-1 fecal curve only 100 days before collections were terminated. Although the value shown in Table XIII, 650 days, was fitted to the data by least suqares, it is uncertain. However, this portion of the Cal-1 fecal curve was almost parallel to the urine curve, US = 475 days, which is encouraging. The value chosen for FS_5, 4000 days was obtained by least-squares fitting the fecal data of the 0.1 μCi/kg group of Utah dogs from

750 through 1750 days postinjection.*

Evaluation of coefficients

The intercepts of the first two components of the normal fecal Pu curve are the mean values of FA_1 and FA_2 determined for the group of persons whose gastrointestinal tracts were judged to be normally stimulated and normally functional. The intercept of the third component, FA_3, is the mean of the four Pu(IV)-injected cases for whom that parameter could be estimated.

Values for the intercept of the longest observed component, FA_4, were available from only two Pu(IV)-injected persons, neither of whom were considered to have normally functioning gastrointestinal tracts. The last 40 days of fecal collections from Chi-1 were only one-half normal bulk, and he was near death from metastases of his malignancy. Fa_3 taken from his fecal curve was one-half that either observed or estimated for the less seriously ill Pu(IV)-injected persons.

The value obtained for FA_3 from the fecal curve of Cal-1 was even lower -- slightly more than 50% of FA_3 for Chi-1, and 20% of the average FA_3 of the Pu(IV) group. His stomach had been completely removed four days after the Pu injection. He was postoperative and mildly anemic during the enitre period of fecal collections.** In the absence of a stomach, his daily food intake was probably low, and gastric juice -- which makes up a significant fraction of the total volume of digestive secretions -- was absent. Gastric acid is one of the normal stimulants of the secretion of bile, pancreatic and

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*Feces were collected periodically from some of the 0.1 μCi/kg dogs for as long as 2921 days.[29] Data for individual dogs as well as the mean values of all survivors exhibited a rising trend after 1800 days.

**The original reference[57] states that fecal and urine samples were oven-dried, treated with conc. HNO_3, redried, and then dry-ashed in a furnace for 4 hours at 500° C; and that the resulting ash was soluble. One of the authors recalls that the published prodecure yielded completely soluble urine samples but that evidently in their hurry to publish the results they failed to remark upon the presence of insoluble residue in fecal samples. In addition, after 30 days the individual himself collected all the samples in his own home wihtout supervision, so some sample loss is possible. Thus it is likely that some fecal Pu was not recovered, leading to a further systematic reduction of the measured fecal Pu output by this individual.

intestinal juices, and intestinal mucus.[98] [101] Iron absorption is reported to be reduced by as much as 50% after gastrectomy.[93] Lack of gastric juice may have played an indirect as well as a direct role in reducing the quantity of gastrointestinal secretions and concomitantly the amount of fecal Pu.

It was assumed that the relationships between the Fa_3's of Chi-1 and Cal-1 and the Pu(IV)-injected group,

$$FA_3(\text{Chi-1}) = 0.5 \times FA_3[\text{Pu(IV)}], \quad FA_3(\text{Cal-1}) = 0.21 \times FA_3[\text{Pu(IV)}],$$

could be used to estimate FA_4 for the Pu(IV)=injected group as follows:

$$FA_4 = [(0.0018/0.5) + (0.0056/0.21)] + 2 = 0.003 \ \%/\text{day}.$$

An approximation of FA_5 was obtained by assuming that F_5 in the human curve and in the dog curve emerged at about the same time postinjection. F_4 was extrapolated to that time (900 days), a line of 4000-day half-time was drawn through the 900-day point and its intercept was determined to be 0.0012 %/day.

The parameters of the equation of the Pu fecal excretion curve for normal man are given in Table XIV along with the equations for the dog and pig.

Table XIV. Fecal Excretion of Pu by Adult Man, Young Adult Beagle, and Adolescent Hormel Miniature Pig. Parameters of exponential fecal excretion equations.[a]

	$F\alpha_1$ (%/day)	FT_1 (days)	$F\alpha_2$ (%/day)	FT_2 (days)	$F\alpha_3$ (%/day)	FT_3 (days)	$F\alpha_4$ (%/day)	FT_4 (days)	$F\alpha_5$ (%/day)	FT_5 (days)
Normal man[b]	0.60	2.0	0.16	6.6	0.012	56	(0.002)[c]	380	(0.0012	4,000)[c]
± S. D.	0.28	0.9	0.11	2.7	0.003	6				
Dog[d]	3.00	2.3	0.31	4.6	0.08	14	0.007	350	0.0046	3,850
Pig[e]	0.37	1.5	0.18	10.0			0.012	325		

[a] F_t (%/day) = $\sum_{n=i}^{n} F\alpha_i \exp(-0.693t/FT_i)$.

[b] Liver and digestive tract functions presumed to be within normal limits.

[c] Estimated; see text.

[d] Stover et al.[29], and B. J. Stover and D. R. Atherton, original data; 0.1 μCi/kg and 0.3 μCi/kg groups only.

[e] Data read from Fig. 1 of Clarke et al.[40]

URINARY AND FECAL CLEARANCE OF PLUTONIUM

Having no fecal data beyond 138 days, Langham et al.[19] were forced to use an estimate of the Pu U/F ratio to calculate long-term Pu excretion. However, both terms of the U/F ratio are subject to change, and clues to the nature of some changes -- either in excretory efficiencies or in the chemical state of circulating Pu -- can be obtained from plasma clearances. Accurate determination of urinary clearance requires simultaneous sampling of plasma and bladder urine. Painter et al.[14] measured urinary Pu clearances of dogs injected with acutely toxic toses of Pu(VI) citrate. In the absence of such precise measurements for man, equations (5a) and (5b) given below, were used to estimate excretory clearances from the data available for man, namely, intermittent plasma samples 24-hour urine samples, and pooled fecal specimens.

$$U_{cl} = \frac{\sum_{t_1}^{t_2} U}{\int_{t_1}^{t_2} P(t)\,dt}, \quad (5a) \qquad F_{cl} = \frac{\sum_{t_1}^{t_2} F}{\int_{t_{1-1}}^{t_{2-1}} P(t)\,dt} \quad (5b) \quad \text{where}$$

$$P(t) = \sum_{P_i=1}^{P_i=n} (P_i e^{\lambda_i t}).$$

Both urinary and fecal clearances were calculated over 6-day intervals for as long as blood measurements were made, but only two intervals, at the beginning (1 to 6 days) and the end (19 to 24 days) of measurements are shown in Table XV.

Painter et al.[14] found that urinary clearance of Pu was very high 15 to 30 minutes after intravenous Pu(VI) citrate injection into dogs. Urinary clearance dropped rapidly to a minimum which persisted from 4 hours to the end of the first day. After the first day urinary clearance rose slightly to a level that was sustained for the next 15 days.

Table XV. Renal and Gastrointestinal Clearance of Circulating Pu. Clearances are expressed as fraction of circulating Pu.

	Renal Clearance			Fecal Clearance			(U/F)[a]		
	Group[b]	1 to 6 days	19 to 24 days	Group[c]	1 to 6 days	19 to 24 days	1 to 6 days	19 to 24 days	35 to 65 days
HP-1	A	0.008		R	0.009		0.9		
HP-2		0.017	.031		0.020	0.061	0.8	0.5	
HP-3		0.020	.070	Ab.L.	0.011	0.037	1.8	1.9	
HP-4	Ab.K.	0.009	.029		0.010	0.030	0.9	1.0	
HP-5		0.021	.098		0.034	0.095	0.6	1.0	
HP-6		0.020	.130		0.020	0.100	1.0	1.3	
HP-7	A	0.011	.025	R	0.008	0.027	1.4	0.9	
HP-8		0.019	.066	R	0.017	0.056	1.1	1.2	1.3
HP-9	A	0.007	.034		0.024	0.055	0.3	0.6	
HP-10		0.013	.090	R	0.0060	0.051	2.2	1.8	
HP-12	A						0.4	0.7	1.2
Kidney and erythropoiesis normal				G.I. function normal					
Mean		0.018	.081	Mean	0.022	0.068			
± S. D.		0.003	0.034	± S. D.	0.009	0.029			
Anemia and/or abnormal kidney[b]				Restricted diet and/or abnormal liver					
Mean		0.0088	.029	Mean	0.010	0.034			
± S. D.		0.0007	.004	± S. D.	0.004	0.017			
"P"[d]		0.01	0.02	"P"	0.02	0.05			

[a]U/F calculated from ratios of plasma clearance except for HP-12 and values obtained after 35 days for HP-8, which are ratios of summed excreta.

[b]Discussion of medical status groups in section on urinary excretion. A = anemic, Ab.K. = abnormal kidney.

[c]Discussion of medical status groups in section on fecal excretion. R = restricted diet, Ab.L. = abnormal liver.

[d]T - test of Fisher[91].

The urinary Pu clearances calculated here for man revealed a similar pattern. The very high initial clearance could not actually be demonstrated, because the earliest urine samples were pooled for the first 24 hours. However, the first 12 urine specimens passed by Chi-1 were analyzed separately, and 83% of the Pu excreted in the first 48 hours was passed in the first (0- to 6-hour) specimen.[47] In the face of his rapidly declining blood level[18] (also see the section on Pu in the circulation), this large urinary output would indicate a high initial Pu clearance.

In every case the average Pu clearances by the kidney and the gastrointestinal tract were lowest on the first day after injection (the minimum lasted through the third day for fecal clearance in some cases because of fecal lag). Clearance by either route rose to a temporary plateau, better defined in some cases than others, of 5 to 15 days duration, and was followed by either another increase to a fairly stable plateau or a continued slow increase to the end of measurements between the twentieth and thirty-fifth day. During the 2 weeks between the two sets of calculations shown in Table XV both urinary and fecal clearances increased, so that by 19 to 24 days after injection Pu excretion by either route was 3.7 times as efficient as it was during the first 6 days after injection.

Renal Pu clearance in those persons judged to be anemic was less than one-half that in persons considered normal as shown in Table XV. Fecal clearance in those persons judged to have reduced digestive-system function was less than one-half that of persons considered to have normally stimulated gastrointestinal tracts. Because of the small groups and the wide ranges of values among the so-called normal persons, the difference was significant only for the first 6 days' urinary excretion.

Ratio of urinary to fecal Pu

Urine to fecal ratios (U/F) were calculated for each case during the

two intervals shown in Table XV, using plasma clearances whenever possible. The late value of U/F calculated for HP-8 and the three U/F values shown for HP-12 were calculated from summed excreta over the intervals indicated. The spread of U/F values was wide -- nearly sevenfold. A total of 23 U/F determinations was available from the Pu(IV)-injected individuals -- 11 determinations during the interval 1 to 6 days, 10 determinations during the interval 19 to 24 days, and two determinations over 10-day intervals between 35 and 65 days after the Pu injection. Of these 23 U/F values, 13 were close to 1.0 (0.7 to 1.3); five were substantially less than 1.0 (0.3 to 0.6); and five were substantially more than 1.0 (1.4 to 2.2). Six U/F values were obtained from the three persons judged to be most nearly normal with respect ot both latent transferrin binding capacity and digestive-system function (HP-2, HP-5, and HP-6). Four of the six U/F values from this normal group lay between 0.8 and 1.3, and the other two U/F values were less than or equal to 0.6. Of the five U/F values greater than 1.4, all were from persons with supressed or impaired digestive-system function (HP-3, HP-7, and HP-10). There were not enough cases to permit examination of the influence on the U/F ratio of anemia alone, but two of the four values of U/F less than 0.6 were from an anemic individual.

The two U/F values obtained from this group of Pu-injected persons more than 30 days after injection were from HP-8, an individual who presumably had been on a restricted diet at the time of injection, and from HP-12, an individual who was recovering from acute anemia caused by hemorrhage. By 35 to 65 days postinjection both may have been approaching normal with respect to protein binding (HP-12) and gastrointestinal secretion (HP-8). The only long-term excretion data are the measurements from Chi-1 and Cal-1, and their U/F results have been rejected for the same reasons that their

fecal excretion was considered unusually low (see the preceding section, on fecal excretion).

It appears that during the first 30 to 60 days after Pu injection the U/F ratio for those persons judged to be most nearly normal was about 1.0 and possibly as great as 1.3. The anemic cases with normal gastrointestinal function (HP-9, HP-12) tended to have a U/F value less than 1.0. Those persons with presumably normal plasma protein binding capacity but with reduced gastrointestinal function (HP-3, HP-10) tended to have U/F values greater than 1.0. The anemic cases [in which protein binding capacity was presumed to be elevated and gastrointestinal secretion was also presumed to be suppressed (HP-1, HP-7)], exhibited reduced urinary and fecal clearances of Pu, and their U/F values were again close to 1.0.

Langham et al.[19] used Pu U/F ratios varying from 1.8 at 138 days to 4.4 at 1750 days to estimate total long-term Pu excretion, but these U/F estimates were based entirely on data from Chi-1 and Cal-1, both of whom have been considered in this reanalysis to have subnormally stimulated or subnormally functioning gastrointestinal tracts. The analysis presented here indicates that immediately after injection in man, Pu excretion in feces slightly exceeded Pu excretion in urine, and that by the end of the second week excretion by the two routes was nearly equal provided that residual transferrin binding, kidney function, liver function, and gastrointestinal secretion remained within normal limits. Comparison of the coefficients of the long-term components of the exponential urinary and fecal Pu-excretion equations (see Tables X and XIV) suggests that at times after Pu injection longer than 100 days, U/F for Pu in man probably lies between 1.0 and 1.5.

Long-term excretory clearances of Pu in man and animals

Stover et al.[28] using power-function equations for Pu in plasma and urine (obtained by combining data from all dose levels) calculated long-term urinary Pu clearances for their dogs. From 22 days to 4 years urinary clearance

was 7.5% to 9% of circulating Pu. Fecal clearance was not calculated, but the long-term F/U ratio of 1.4 implied a fecal clearance range (again for all dose levels combined) of 10.5% to 12.6% of circulating Pu. Urinary and fecal Pu clearances have been recalculated here only for the group of dogs receiving 0.1 μCi/kg, the lowest Pu dose level for which long-term plasma and excretion data are available. Using the exponential parameters in Tables V, X, and XIV and Eq. (5a), urinary and fecal clearances were calculated every 50 to 100 days for the interval 50 to 600 days (for eventual comparison with the pigs). The average urinary and fecal Pu clearances thus calculated were 11.6% and 10.9% respectively of circulating Pu. The differences between these values and those of Stover et al.[28] -- higher urinary clearances and equal urinary and fecal clearances -- appear to be mostly the result of exclusion of the higher-dose-level dogs, in which liver and bone damage occurred after the first year.

Excretory clearances were calculated in a similar way for the pig, using Eq. (5a) and the exponential parameters shown in Tables V, X, and XIV. There were no plasma Pu measurements recorded before 27 days, and measurements were terminated at 470 days, so clearances were calculated only for the interval 50 to 100 days and for 100-day intervals from 100 to 300 days.* Average urinary and fecal clearances over the interval 50 to 300 days were 9.8% and 2.8% of circulating Pu, respectively. Urinary clearance was about the same as that calculated over this interval for the dog and slightly higher than calculated at 3 weeks for man, but the fecal Pu clearance of the pig was much lower than that of the other species. Anatomically the porcine liver differs slightly from the livers of dog and man; however,

*Tests of the dog data showed that lack of longer-liver components in either the plasma or excretion equations led to substantial errors in calculated clearances at times longer than one half-time of the last available component of the excretion equation.

this difference is not known to be related to function.

There are no late plasma data from which to calculate long-term Pu clearances for man, but the animal data provide some clues. The coefficient of the last measured component of the human Pu plasma equation is greater than the sum of the long-term coefficients of the Pu plasma curve of the dog (low dose levels only), and at the same time the sum of the late coefficients of the human excretion equations are less than those of the dog. It would appear that at long times after Pu injection, Pu clearances by the human kidney and gastrointestinal tract are (a) either equal to or less than those calculated for the first 3 weeks, and (b) either equal to or less than (but certainly not greater than) the excretory clearances calculated for the dog.

Some thoughts on the mechanisms of Pu excretion

In the dog and apparently also in man, Pu clearance is most efficient in the first few minutes after injection, at which time a significant fraction of Pu (about 50% in the dog[33])* has not yet been protein bound. Minimum excretory clearances were found to coincide with time of maximum Pu-protein binding (in the dog about 95% of Pu was protein bound 7 hours after injection[33]).* By the end of the first day after injection the fraction of Pu circulating bound was possibly slightly greater. The data of Stevens et al.[33] suggest that less then 10% of circulating Pu was associated with a low-molecular-weight fraction 7 days after injection. Within 2 weeks after injection both the renal and gastrointestinal clearances calculated for man increased four-fold. If Pu protein binding in human plasma occurrs to the same degree as in the dog, one would not expect any changes in Pu excretory clearances.

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*Fractional Pu-protein binding was estimated from the relative heights of the elution peaks in Fig. 2.[33]

Current knowledge suggests that some Pu, (presumably circulating as a low-molecular-weight compound) is cleared by the kidney and gastrointestinal tract in the usual sense of being moved across cell membranes without participating in any process other than transport. But if these mechanisms -- renal filtration and secretion in digestive juices (like calcium[102]) --- were the only ways Pu could be eliminated, then Pu excretion should remain at the low level observed after the first postinjection day and should be roughly similar for most species over a wide range of physiological conditions. Delayed excretion of some Pu initally deposited in renal and intestinal tissues* would account for only a temporary rise in excretory efficiency.

Feedback from bone and tissues of a more readily filterable form of Pu seems unlikely. During the interval 100 to 600 days after injection, adolescent pigs[40,41,103] lost a net of 53% of the Pu initially deposited in their skeletons. During the time Pu was leaving the skeleton, the plasma Pu level was sustained, and renal excretion was high; but fecal clearance remained low, and renal clearance was the same as it had been in the 50 days preceding the start of bone Pu release. Throughout the experiment the renal Pu clearance of the pigs remained constant and was similar to the renal clearances of the dog and of man. These observations imply that Pu released to the circulation in the course of bone remodeling is associated with plasma proteins to the same extent as was the Pu originally injected.

The excretory clearances of Pu in the normal people rose during the first 3 weeks after injection. During that same time, in the dog, there was no apparent change in the fraction of unbound Pu in the plasma.[33] Further, it does not appear likely that Pu recirculated from bone exists in a more filterable

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*Autoradiographs of mouse kidney and intestine showed that shortly after intravenous or intramuscular injection Pu was present at high concentrations in the renal papilla and the lamina propria and submucosa of the intestine. These concentrations were nearly gone 30 to 60 days later.[104]

form in plasma. By analogy with iron, a significant fraction of Pu must be eliminated by cellular mechanisms involving the Pu-transferrin complex. These might include incorporation into and subsequent loss with exfoliating cells, especially those of the intestinal epithelium, or release during catabolism of the protein moiety of the Pu-transferrin complex in the intestine and kidney, or both mechanisms.

The Pu clearances of the animals raise some interesting questions: Why is the Pu fecal clearance of the pig so low? Why are the Pu excretory clearances of the dog higher than those of man? Some tentative answers can be supplied from what is known or suspected about (a) the iron intakes of the species, and (b) the regulation of iron absorption and excretion. There is general agreement that regulation of iron absorption and excretion is accomplished by the gastrointestinal tract.[90,92,93] The information reviewed here indicates that the mechanisms of Pu excretion resemble those described for iron, so much so that Pu may be regarded as a tracer of iron excretion (as well as iron transport).

During growth iron balance is positive-- absorptive mechanisms are promoted and excretion is supressed.[93] Supression of iron excretion (and with it Pu excretion) is one possible reason for the low fecal Pu clearance in the adolescent pigs. Wild pigs are scavengers feeding mostly on vegetable matter, grubs, insects, etc. They encounter muscle meat only occasionally as carrion. Except in areas where the soil has high iron content, the natural diet of the pig can be considered to be low in iron. As a consequence of this dietary history, the domestic pig probably conserves iron, most likely by secreting very little in bile. Impairment of Pu excretion would be expected if one of the mechanisms for iron excretion were supressed or absent.

Iron is stored in two forms, as soluble dispersed ferritin and as insoluble aggregates of hemosiderin.[36,90,92-93] It is believed that the labile

storage pool of soluble ferritin in the liver is the source of biliary iron.[36] The one-way nature of the iron storage system is demonstrated by failure of an ^{55}Fe tracer to equilibrate with stored iron even after several years.[105] Recent studies by the Utah group[106, 109] suggest a similar liver-storage pathway for Pu. Pu initially deposited in liver is associated with soluble ferritin, but after 30 to 60 days a large fraction of liver Pu is insoluble. The rapid transition to insoluble forms that are less amenable to elimination* is substantiated by the rapid decline in fecal Pu excretion by the dogs. The iron-rich natural diet of dogs (red meat, blood, and organs) and their high gastric acidity (which acts to promote iron absorption[93]) suggest that some of the parameters of iron metabolism in the dog may not be the same as those of man. Transferrin saturation in man is elevated in conditions of iron overload.[36] With a higher iron intake and potentially more efficient iron absorption, transferrin in dog plasma may normally be more saturated than that in human plasma resulting in reduced Pu-protein binding and greater Pu excretion in urine and digestive secretions of the dog. As a normal measure to prevent iron overload, the canine liver may excrete more iron in the bile than does the human liver. Both mechanisms would tend to suppress iron absorption and enhance iron excretion by the dog, and both would contribute to greater efficiency in Pu excretion observed in the species.

Much of the content of the above paragraphs is speculation. However, the details of human Pu excretion are few, and additional information on Pu excretory mechanisms in man may not be available for a long time to come. Careful investigations of comparative Pu excretory mechanisms and of comparative iron metabolism in several species, to fill some of the knowledge gaps in human Pu experience, are clearly indicated.

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*At high Pu dose levels there was severe liver damage and loss of a large fraction of the early liver deposit.[106] In those dogs fecal excretion remained high, and fecal clearance was higher than urinary clearance.[28]

HUMAN PLUTONIUM EXCRETION--COMPARISON WITH PREVIOUS ANALYSES

When excretion rates are expressed as sums of exponentials, urinary excretion at time t after injection is

$$U_t \ (\%/\text{day}) = \sum_{n=i}^{n} U\alpha_i e^{\underline{0.693}/UT_i}, \qquad (6)$$

and similarly, fecal excretion rate at time t is

$$F_t \ (\%/\text{day}) = \sum_{n=i}^{n} F\alpha_i e^{-0.693t/FT_i}. \qquad (7)$$

The total amount of Pu excreted in urine or feces at time t is obtained by integration of Eqs. (6) and (7).

$$\Sigma \ U_t \ (\%) = \int_0^t U_t dt, \qquad (8)$$

$$\Sigma \ F_t \ (\%) = \int_0^t F_t dt. \qquad (9)$$

Total excretion at time t is the sum of Eqs. (8) and (9).

$$\Sigma \ E_t \ (\%) = \Sigma \ U_t + \Sigma \ F_t \qquad (10)$$

and whole-body retention at time t is

$$R_t \ (\%) = 100\% - \Sigma \ E_t. \qquad (11)$$

The fraction of the remaining body burden excreted daily in urine at time t is

$$U_b \ (\%) = (U_t \times 100)/R_t. \qquad (12)$$

Urinary and fecal excretion rates (Figs. 7 and 8), total Pu excreted in urine and feces (Table XVI), whole body retention (Fig. 9), and the fraction of the body burden excreted in a 1-day urine sample (Fig. 10) were calculated for times after injection from 1 to 14,600 days (about 40 years), using Eqs. (6) through (12) and the parameters of the

Table XVI. Comparison of Long-term Pu Excretion Predicted From Power Function or Sums of Exponentials.[a]

Time after injection (days)	(years)	Pu excreted (% of dose) Power functions, Langham et al.	Sums of exponentials, this paper
10		2.56	4.39
20		3.17	5.25
40		3.81	5.95
60		4.21	6.35
80		4.50	6.67
100		4.74	6.96
140		5.10	7.39
360	1	6.26	8.79
720	2	7.22	10.23
1,100	3	7.83	11.17
1,500	4	8.30	12.24
1,800	5	8.68	13.00
3,650	10	9.96	15.47
7,200	20	12.17	18.83
14,600	40		22.49

[a]See Tables X and XIV for excretion equation parameters.

normal Pu urinary and fecal excretion equations given in Tables X and XIV. It was assumed for these calculations that an additional component (the sixth) with a half-time of 13,400 days (see the discussion of accident case LASL-1 in the section on urinary excretion) emerged in both excretion curves about 4000 days after injection. Total Pu excretion after a single intravenous injection predicted by the sums of exponentials derived in this paper is compared in Table XVI with Pu excretion predicted by the power functions originally derived by Langham et al.[19] Sums of exponentials predicted greater Pu elimination at all postinjection times for at least three reasons: (a) Exponentials fitted the first 10 days' data better than the power functions. (b) Only the individual urine-curve and fecal-curve coefficients from cases judged to be normal with respect to the particular excretory function were used to calculate the mean coefficients of the exponential equations, and they tended to be higher than the averages of all cases. (c) The coefficients of the exponential equation of human fecal excretion were adjusted upward to correct for what was considered to be unusually low long-term fecal elimination by Chi-1 and Cal-1.

For easier comparison with earlier analyses, the urinary and fecal excretion rate equations (in Tables X and XIV) are replotted logarithmically in Figs. 7 and 8. At least three power functions were needed to describe these equations. The power function fitted to the calculated urinary excretion in the time period from 30 to 360 days was almost the same as that originally derived by Langham et al.[19] from the raw averages of the data from the Pu-injected cases and some accidentally

exposed Los Alamos personnel, and more recently reevaluated by machine-curve fitting by Robertson and Cohn.[25]

This paper, U_t (%/day) = $0.17T^{-0.725}$ ($30 \leq T \leq 360$ days)

Langham et al.[19] Y_{ua} (%/day) = $0.2X^{-0.74}$ ($10 \leq X \leq 1750$ days)

Robertson and Cohn,[25] Y_u (%/day) = $0.193t^{-0.721}$ ($1 \leq t \leq 1750$ days)

Fig. 10 is the log-log plot of the fraction of the remaining Pu burden excreted daily in urine. The power function fitted to the time period $40 \leq T \leq 360$ days is again nearly the same as that derived by Langham et al.[19] using a different analytical method.

None of the power functions needed to fit the values of human Pu fecal excretion calculated from the exponential equation in Table XIV (see Fig. 8) agreed with the expression derived by Langham et al.[19]--probably for the same reasons as listed above for the discrepancies between the two methods of predicting long-term total Pu excretion. Most of the difference between the two methods arises from the ways fecal data were handled and the assumptions about the long-term trend of fecal Pu output.

PREDICTION OF LONG-TERM WHOLE-BODY PLUTONIUM RETENTION

The currently accepted limits of human Pu contamination appear in the joint report of the Internal Dose Committees of the International Commission on Radiological Protection and the United States National Committee on Radiation Protection, issued in 1959.[64] The maximum permissible ^{239}Pu contents of the body based on skeleton and liver of occupational workers are given as 0.04 and 0.4 μCi, respectively. For purposes of dose calculations biological half-lives are also given; 6.5×10^4 days (178 years) for the whole body, 7.3×10^4 days (200 years) for skeleton, and 3×10^4 days (82 years) for the liver. These values were based on the original analyses of the human Pu data by Langham et al.,[19,20] who estimated that the longest half-time of Pu in the whole body lay between 85 and 175 years. The lower limit was adopted in the ICRP-NCRP report as the half-time of Pu in the liver. The upper limit was assumed to represent Pu in the whole body. The upper limit rounded off upward was adopted as the half-time of Pu in the human skeleton, and the lower limit was adopted as the half-time of Pu in human liver. Use of the term "retention" is potentially misleading. Retention suggests a static condition, once deposited in a tissue Pu would be understood to remain fixed until eliminated from the body altogether. Whole-body retention further would suggest that Pu is eliminated from all tissue deposits at comparable rates. Studies of pigs and dogs show some important features of Pu metabolism that appear applicable to Pu metabolism in man, but even more importantly, they demonstrate the dynamic behavior of Pu.

Pu turnover in animals

Pu metabolism was followed after injection of Pu(IV) citrate in

adolescent miniature swine.[40,41] (Swine were yearlings. This term is usually applied to animals 1 to 1.5 years of age (L. K. Bustad, private communication). Miniature swine achieve adult body size between 2.5 and 3 years of age,[103] and yearlings can be considered to be comparable to human adolescents.) In the course of 600 days of growth remodeling, their skeletons released about 38% of the injected dose (53% of the 30-day bone deposit). Plasma Pu level and urinary excretion of Pu remained high. At 600 days the liver contained three times as much Pu (35% of the dose) as it contained 30 days after injection (13% of the dose).

The lower-dose groups of dogs in the Utah experiment are now yielding long-term results. At this writing there have been enough deaths of dogs injected with 0.3 μCi/kg or less to demonstrate that skeletal Pu retention is not affected by dose level below 0.3 μCi/kg and to establish a long-term half-time of > 1500 days for Pu in the beagle skeleton.[110] Jee et al.[111] examined the disappearance of Pu-labeled trabecular surfaces of dogs given Pu doses of 0.015 and 0.3 μCi/kg. They found 50% to 64% of trabecular surfaces labeled in vertebral bodies and femoral metaphyses, respectively, 5 days after injection of Pu. Three months later 0.2% to 3.3% of vertebral trabecular surfaces were labeled, and 14% to 20% were buried by new bone; 0.7% to 3.3% of femoral metaphyseal trabecular surfaces were labeled, and 24% to 48% were buried by new bone. These observations show the enormous turnover of trabecular surfaces in these two anatomical locations in the young adult beagle skeleton.

The long-term Pu content of the livers of the low-dose dogs has also been examined. At levels less than or equal to 0.1 μCi/kg of Pu, net loss of Pu from the liver was found to be much less than was originally predicted from high-dose animals. At the low dose levels, the half-time

of Pu in the liver was about 3800 days,[113] more than or the same as Pu half-time observed in the skeletons of these same dogs. The prolonged residence in liver seems to be the end result of a chain of events that carries Pu from Pu-transferrin in plasma, to Pu-ferritin in hepatic cells, and eventually to long-lived deposits of Pu-hemosiderin in reticuloendothelial cells.[106-108]

Pu dynamics can be generally summarized as follows: Pu initially present in soft tissues other than liver is cleared rapidly; the major fraction is redistributed to bone and liver, and a small fraction is excreted. Pu deposited in the skeleton is mobilized in the normal course of bone remodeling; some is redeposited in bone, some is deposited in liver, and a small fraction is excreted. Pu deposited in liver is eventually transformed from relatively soluble forms in hepatic cells into insoluble hemosiderin deposits and sequestered in reticuloendothelial cells. Therefore, liver Pu is likely to be lost more slowly than bone Pu, but at perhaps the same rate as deposits of phagocytized Pu-hemosiderin in other tissues. The loss rate from the liver may eventually become the rate-limiting process for Pu disappearance from the whole body.

The half-times of the earliest components of the plasma and excretion curves are similar for the three species studied - dog, pig, and man (see Tables VI, X, and XIV). By analogy with iron metabolism, these components may represent such processes as the incorporation of Pu into and subsequent shedding of intestinal epithelium, and the destruction of the protein portion of the Pu-transferrin complex. The slower components are evidently the result of Pu feedback -- early from soft tissues and later from bone -- and reflect the intrinsic turnover rates of these tissues (either the cells themselves or their mineral content) distorted

by redeposition. The effect of redeposition is to reduce the net turnover of the nuclide in question.[113] The observed or effective half-time, $T_{1/2\ obs}$, is related to the half-time of tissue turnover or physiological half-time, $T_{1/2\ phys}$, and to the fraction of circulating radionuclide that is redeposited, fr:

$$T_{1/2\ obs} = T_{1/2\ phys}/(1 - fr). \qquad (13)$$

Pu turnover in human soft tissues

The best estimates of the early distribution of Pu in four major compartments - skeleton, liver, residual soft tissues, and excreta - are shown in Table XVII for man, dog, and pig. The original analysis of the tissue distribution data by Langham *et al.*[19] is included for comparison. The pigs were not fully grown and the dogs were 1.5 years old (in the prime of young adulthood), in contrast to the Pu-injected human beings, who were all unwell, and except for HP-4, middle-aged or older. In the dog only a small fraction of the Pu dose was in soft tissues other than liver 21 days after the injection.[28] The value shown in Table XVII for the pig is uncertain. It was obtained by difference, using bone and liver determinations from two separate experiments.[40,42] Even so, the calculated value of 8% for Pu in soft tissues at 30 days is lower than the 12% average soft-tissue Pu in the Pu-injected people who came to autopsy 5 to 15 months after injection.

The half-times of the two-component exponential equation fitted to the human soft-tissue data (see Fig. 1) were 7.2 and 480 days. The first is roughly the same as the early soft-tissue clearance in several animals. The second component, although its half-time is not so long as that measured in the dogs, involves a significantly larger amount of the injected

Table XVII. Early Distribution of Pu in Man, Dog, and Pig.

	Time after injection	Pu content (% of dose) Skeleton	Liver	Soft tissue remainder	Excreta
Man					
This paper	5 to 17 days[a]	47.5	26.8	23.3	2.4
	5 to 15 months[b]	47.5	31.2	11.2	9.5
Langham et al.	4 to 457 days[c]	65.7	22.5	6.8	5.0
Dog[d]	22 days	54.0	31.0	3.0	12.0
Pig[e]	30 days	72.0	14.0	8.3	5.7

[a]Average of Cal-1, Chi-2, HP-11, Cal-3. Livers and skeletons of Chi-2 and HP-11 not included. See Tables I and IV.

[b]Averages of HP-5, HP-9, and Chi-1. See Tables I and IV.

[c]Average of all tissues from all cases in Langham et al[19]. Excretion estimated from power functions. Soft tissues calculated by differences.

[d]Skeleton, extrapolation of curves for 0.3 μCi/kg group.[110] Liver, extrapolation of curves for 0.3 μCi/kg group[60]. Soft tissue and excreta from Stover et al.[28]

[e]Skeleton from Clarke et al[40]. Liver from Smith et al [42]. Excreta calculated from exponential equations in Tables X and XIV. Soft tissue calculated by difference.

Pu. A component with a half-time of the same order of magnitude, about 300 days, appears (perhaps fortuitously) in both the human urinary and fecal excretion equations but is missing from the excretion equations for the dog and pig. The large size of the soft-tissue compartment in these middle-aged people compared with the much smaller soft-tissue compartment in the young vigorous animals may be related to species differences, or it may be a real effect of age stemming from poorer circulation, more fibrous (less cellular) connective tissue, the presence of ectopic calcification and fatty plaques, and reduced cell turnover that accompany advancing age.

Pu turnover in human bone

The turnover rate of the adult human skeleton is not known. Net turnover of bone Pu in the adolescent pigs was calculated to be 52%/year,* and that of the young adult dogs, to be 17%/year.* Assuming a constant redeposition in bone of 60% of circulating Pu and using Eq. (13), one can estimate the turnover rates of the bone containing the Pu, (most likely the labeled surfaces), to be respectively 140%/year and 68% year in the adolescent pigs and young adult dogs. Turnover of both the Pu and the Pu-containing bone of middle-aged human beings is most certainly slower than for the young experimental animals.

Frost,[114] using a tetracycline labeling material, estimated the rate of replacement in rib and clavicle cortex of persons 35 to 70 years of age to be between 2.5%/year and 6%/year. Kulp et al.[115] used fallout

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* Pig: (0.693 times 365 days/year)/480 days = 52%/year.

* Dog: (0.693 times 365 days/year)/1,500 days = 17%/year.

^{90}Sr analyses of individual bones and whole skeletons to obtain specific activity ratios (^{90}Sr in bone/^{90}Sr in skeleton) in adult human bones of 0.45, 1.4, and 2.1 for long-bone cortex, whole rib, and vertebrae, respectively. Bryant and Loutit[116] made similar measurements on adult human bones and obtained nearly identical specific activity ratios. From these data they calculated the annual rate of bone turnover required to produce the observed specific activities -- 1.1%/year to 2.6%/year in whole femur, 2.1%/year to 6.2% /year in whole rib, and 5% /year to 10.4%/year in vertebrae. Rowland,[117] using an autoradiographic technique and bone from persons with long-standing burdens of ^{226}Ra, calculated a turnover rate of 1.1%/year for long-bone cortex.

All the above calculated turnover rates are in good agreement with each other. The good agreement between the isotopic methods[116] that are known to be distorted by redeposition and the tetracycline method[114] in which redeposition is not a factor indicate that the isotopic measurements with ^{90}Sr and ^{226}Ra are not significantly distorted by redeposition and are probably close to actual rates of bone turnover. A comparative metabolic study in an elderly human male by Mays et al.[118] indicates that long-term redeposition of ^{90}Sr is not more than 15%, and ^{226}Ra redeposition is not more than 5%.

The best estimates of the annual replacement rates of certain human bones are probably the mid-points of the ranges cited above -- 1.85% year for whole long bone, 4.2% /year for whole rib, and 7.7% /year for vertebrae. These are mass or volume replacement rates, and Pu is deposited on bone surfaces. May[119] suggested a technique to relate bone surface to volume that did not require knowledge of the absolute values of the bone

surfaces. He estimated that for a given mass of trabecular bone the surface was four times that of the same mass of cortical bone. Using that ratio, 4:1, for trabecular to cortical bone surface, estimating trabecular bone mass to be 23% of the total (ashed or dried) skeleton, and using the above cited estimates of bone turnover, one calculates the average turnover rate of the bone surface of the entire human skeleton to be 5% /year (0.23 × 4 X 7.7%/year) + (0.77 × 1.85% /year) = 5% /year). The associated half-time of the bone surfaces is 13.9 years, slightly less than the 15-year half-time observed in long-term ^{226}Ra retention in man,[120] and slightly more than the half-time for human bone surface replacement, 10.8 years, that can be calculated from the dog data and the comparative life spans of the two species.*

Assuming that 60% of circulating Pu is redeposited in bone, the observed half-time of Pu in the human skeleton would be 35 years (12,700 days), perhaps fortuitously close to the 13,400-day half-time that could be fitted to the long-term urine data of case LASL-1 (see section on urinary excretion).

A model of Pu metabolism in man

The half-time of Pu in the human body was estimated in this analysis to be 204 years (from the calculated total Pu excretion in Table XVIII fitted over the interval from 1800 to 14,600 days). This estimate of whole-body Pu half-time is in substantial agreement with the upper limit calculated by Langham *et al.*[19] The half-time of Pu in the human skeleton was estimated to be 35 years. The important consequence of Pu loss from bone

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* $T_{1/2}$ of Pu-labeled dog bone = 1.64 years. $Lifespan_{dog}$ = 14 years. $Lifespan_{man}$ = 100 years. $T_{1/2}$ of Pu-labeled human bone = (100 times 1.64)/14 = 10.8 years.

faster than from the whole body is the increase in liver Pu with time, as shown in Fig. 11. This model of long-term Pu metabolism is in accord with most of the available evidence.

Pu was lost from the skeletons of dogs and pigs more rapidly than from their livers.[40,110,112] In the livers of dogs and rats Pu tends to become sequestered in reticuloendothelial cells chemically combined with insoluble aggregates of stored iron.[106,107,121] Chelation therapy is much less efficient in removing Pu from the livers of pigs and rodents after a lapse of time than it is when the chelating agent is administered shortly after Pu exposure.[42,121,122] As in human experience with cases of iron overload, chelating agents apparently cannot solubilize iron or Pu (or both) stored in liver as aggregates.[36] A variable fraction of human iron stores is very long-lived and to a large degree inaccessible. Radioactive iron tracers do not equilibrate with the iron stores even after periods of many years.[93,105] The only therapeutic measure capable of depleting iron stores in human iron storage diseases is a prolonged series of phlebotomies involving replacement of many blood volumes.[36]

More rapid loss of Pu from bone than from the whole body with net transfer of Pu to the liver is consistent with the results of the long-term PuO_2 inhalation studies in dogs.[123,124] Tissue analyses from dogs killed several years after a single exposure revealed up to two to three times as much Pu in liver as in the whole skeleton.*

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* There is some uncertainty about whether Pu in liver and bone of these dogs has been solubilized and distributed as Pu-transferrin, or whether some PuO_2 can be transferred from lung and tracheobronchial lymph nodes directly to liver in particulate form.

Perhaps even more convincing are the results of tissue analyses of persons who have come to autopsy many years after occupational exposure to Pu. The best documented case is LASL-1, reported by Foreman et al.[58] (also discussed in the section on urinary excretion of Pu). This individual was exposed to high levels of Pu both by inhalation and by contaminated wounds. Examination of his work history, reconstruction of the materials with which he worked, and his working conditions in the middle 1940's strongly suggest that he was exposed early to significant amounts of soluble Pu. Further examination of his work history indicates that the bulk of his exposure occurred in the first two years of his employment beginning at the age of 26 years. He died 12 years later at the age of 38 years in an accident unrelated to his Pu exposure.

Tissue analysis revealed that his terminal Pu content (excluding lung and pulmonary lymph nodes) was roughly 51% in liver and 47% in the skeleton.* The combined Pu activity in the livers and skeletons of the Pu-injected cases was initially partitioned in such a way that 60% was in skeleton and 40% was in liver. The bulk of LASL-1's Pu inhalation exposure and all his Pu-contaminated wounds occurred in the first two years of his employment. Ten years later his Pu exposure can be considered to have been approximately acute. The Pu model predicts that 12 years after an acute exposure to soluble Pu, 48% of the liver and bone Pu will be in liver and 52% in bone. The Pu distribution predicted by the model is encouragingly close to the analytical results. The difference between

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* Total skeletal Pu (including marrow) recalculated for LASL-1, using the ponderal method described in the section on skeletal Pu, was 1.8×10^4 dis/min. Foreman et al.[58] calculated his skeletal Pu content to be 1.4×10^4 dis/min and his liver Pu content to be 1.93×10^4 dis/min.

the predicted and measured values suggests that the model may be oversimplified in that bone turnover is represented by a single term. Some of the bone surfaces of a healthy young adult are certainly being remodeled faster than the whole-skeleton turnover rate of 5%/year used in the model.

Tissue samples have been obtained from persons whose occupations brought them into prolonged contact with small amounts of Pu^{125}. Pu was detectable in at least one of the sampled tissues (lung, pulmonary lymph nodes, liver, and bone (sternum)) in 25 of 41 cases. Liver contained Pu in 21 cases. Lung or pulmonary nodes or both contained Pu in 19 cases. Pu was present in detectable amounts in only one bone sample.* The average length of Pu exposure was 6.3 years for the 25 cases in which at least one tissue contained Pu, and 4.0 years for the 16 cases for which Pu was not detectable. It is also interesting to note that the one case in which Pu was detected in bone died of cirrhosis of the liver, and that Pu could not be detected in his liver sample. Although not providing direct support for the Pu model, these data do not refute it.

There is one case, RF-667, reported by Lagerquist _et al._,[126] that does not fit. This individual was continuously exposed to Pu both by inhalation (chiefly of PuO_2) and through several minor puncture wounds during a 9-year period beginning at 49 years of age. (C. R. Lagerquist and S. E. Hammond, private communication.) Exposure may have been somewhat

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* Skeletal burdens less than 80 pCi were below the analytical detection limit because of small sample size.

greater during the first 5 years. Death occurred from cardiac failure at 58 years. At autopsy there were no gross lesions in other tissues. His terminal body burden of 0.0012 μCi was distributed as follows: 8% in respiratory structures, 8% in soft tissues, 19% in liver, and 65% in skeleton. The amount of Pu in the tissue samples was small, and large analytical errors were possible. There was a fourfold difference in the Pu concentrations of separate rib and sternum samples. Several calculations of his Pu body content from urinalysis using the Langham equation[19] and computer techniques overestimated the Pu found in tissues by a factor of five. The authors suggest that the overprediction of Pu burden by urinalysis may have resulted from his continual exposure pattern. He still had 0.016 μg (0.001 μCi) of Pu in an old finger wound, about equal to what was found in his tissues.

The unduly high urinary excretion (for the size of his body content), the high soft-tissue content, and the discrepancies in Pu content of duplicate bone samples suggest some other possible explanations for the failure of this case to agree with the Pu model. If for unknown reasons his liver was not accumulating and storing Pu released from soft tissues and bone, Pu released from these tissues would be redeposited in them. After 35 years of age bone loss in the human male skeleton (as well as that of the female) progresses sufficiently rapidly to produce by age 60 a significant reduction in the amount of bone in vertebral bodies, rib, and femoral cortex.[128] Thus from age 49 to 58 the preferred Pu deposition sites in bone, quiescent and resorbing sites on trabecular and endosteal surfaces,[127] would appear to be those most likely to be resorbed. In the absence of efficient liver storage of Pu, recirculation from such bone sites would lead to sustained urinary excretion, high soft-tissue

levels, and redeposition in the same potentially short-lived bone sites -- setting the stage for continuous repetition of the entire process.

Mays et al.[129] have calculated that if the body Pu content were partitioned 50% in liver and 50% in bone, the annual risk of developing a liver tumor would be twice that of developing a bone tumor. The long-term Pu distribution predicted by the dynamic Pu model makes it even more urgent that we reexamine the critical organ for Pu. The analysis in this paper suggests that over a 50-year working lifetime the liver's share of the body Pu content grows progressively larger, eventually exceeding 50%. In the younger members of the population avid iron storage and more rapid bone turnover would, according to the model, result in transfer of most of the body Pu to the liver within a few years. The consequence of these calculations and those of Mays et al.[129] is to indicate that liver is probably the critical organ for Pu, and as they have suggested the permissible body content of Pu based on liver as the critical organ may need to be lowered to the same value as (or perhaps less than) the 0.04 μCi presently accepted as the permissible body burden based on skeleton as the critical organ.

Some closing thoughts

In this reexamination of the human Pu data I have tried to present a cohesive working model of Pu behavior that would fit the preponderance of the evidence and not be impeached by seemingly unexplainable discrepancies between prediction and experimental results. The medical histories of the Pu-injected persons revealed some physiological differences that affected their metabolism. Some of the variability in the plasma-disappearance curves, tissue distributions, and excretion patterns of the individuals could be explained in terms of their medical problems, especially those affecting circulation, iron metabolism, and gastrointestinal function. This success led to interpretation of Pu behavior using iron as an elemental model, and opened up what should prove to be a very profitable line of investigation. Some of the troublesome problems in treatment of Pu accident cases might well be examined in light of Pu participation in the iron transport and excretory pathways.

The uncertainties in interpretation of Pu urinalysis are still with us. It is hoped that the evaluation of the human and large-animal excretion data as sums of exponentials, a mathematical form that is easily handled by computer techniques, will inspire others to construct computer simulations of such important problems as multiple exposures, continuous absorption from a wound or lung reservoir, and accident-treatment schedules.

As the writing progressed, it became clear that the original data were good, and that the original analysis was sound. The new data from occupationally exposed persons and from animal experiments, and the use of the iron analogue, contributed more to understanding the old results than did the difference in the analytical approaches. The initial tissue distributions, ex-

cretory patterns, and predictions of long-term Pu elimination presented here do not differ in substance from the original analysis -- only in detail. The collection of human Pu data reported by the Los Alamos group[19,20] contains much more information than was previously supposed, but we anxiously await the results of the current follow-up of Pu workers exposed in the middle 1940's. The long-term dog experiments at Utah, whose 20th anniversary we mark this year have contributed greatly to our general knowledge of Pu, but additional information from these experiments and studies of Pu in other species is needed.

Twenty-six years after they were posed, the questions about Pu metabolism that were put by the Plutonium Project's industrial physicians (see Appendix 1) still have far too few answers. New questions have been raised by the potential world-wide use of Pu as an energy source. Much remains to be done before the Pu story is complete.

Note added in proof: Since this paper was written, Nénot et al[133] have reported that Pu was deposited almost exclusively in the bone of rats injected intravenously with Pu(IV)-transferrin, and Durbin et al[134] concluded from a kinetic analysis of Pu(IV) citrate deposition in the rat that the rat skeleton accumulated both free and protein-bound Pu but that the rat liver did not take up significant amounts of protein-bound Pu. Inasmuch as at times greater than a few hours after injection more than 90% of circulating Pu is protein bound,[33, 89] the deposition pattern of recirculated Pu is more likely to resemble that of Pu-transferrin than that of the Pu(IV) citrate originally injected. Thus, Pu redeposition in bone may be as great as 80% to 90% leading to a longer calculated half-time of Pu in the human skeleton,[113] about 70 years, and to a slower rate of Pu accumulation in the liver.

APPENDIX 1

Summary of Requests for Information Desired Concerning Plutonium

Prepared for a conference on plutonium
held in Chicago May 14, 15, & 16, 1945

Drs. L. H. Hemplemann, S. T. Cantril, J. E. Wirth, J. J. Nickson, and Mr. S. G. English wrote the letters on which this section is based. Immediate problems of importance about which further information is needed are emphasized.

I. Diagnosis and Estimation of the Amount of Plutonium in the Human Body

A. Detection of amounts in the body in excess of the permissible level

1. Development of a satisfactory means of assay of urine and feces

a. Need more information on elimination rate as a function of time

b. Need more information on elimination rate as a function of route of intake

2. Determination of percentage of plutonium excreted daily by humans.

3. Can blood samples be utilized for this purpose?

B. Detection of plutonium in the lung

1. Development of a satisfactory means of estimation of the amount of plutonium in the lung

2. Compounds of interest are +3, +4 nitrate in aqueous solution, +6 nitrate in ether solution, tetrafluoride, +4 oxide, +4 oxalate, +4 peroxide as slurry

C. Development of a method for detection and quantitation of plutonium in wounds

II. Absorption

A. Skin

1. Need more information on absorption rate of various plutonium compounds through the intact skin

2. Is absorption influenced by use of potassium permanganate solution followed by sodium hyposulfate solution on the skin?

B. Gastrointestinal Tract

1. Need more information on absorption rates of various plutonium compounds. Specific information is desired about those compounds mentioned under "diagnosis"
2. Can the elimination of plutonium be used in the event of gross intake to detect the amount that will be fixed in the bone?

C. Wounds

1. The rate of diffusion of plutonium from the wound area
2. The effect of different plutonium compounds on the rate of diffusion
3. How is the distribution pattern altered by having different sorts of wounds, e.g. puncture wounds as opposed to lacerations?

D. Lung

1. How much of the amount breathed is retained in the human lung?
2. How much material is absorbed from the lung to the blood and then to the skeleton?

III. Permissible Levels of Plutonium

A. In the lung

B. In the bone

C. What is the minimum amount necessary to produce damage in the body?

D. Are the rays from plutonium capable of producing damage to the skin?

IV. Metabolism

A. Distribution pattern as a function of rate of intake

B. Distribution pattern as a function of diet

C. What is the rate of elimination of plutonium from bone?

D. Are the differing diets in the different laboratories affecting the results of animal experiments?

V. Pathology

A. What is the nature of liver damage after intravenous administration of plutonium?

B. What is the nature of liver damage after sublethal doses given through other routes of entry?

C. Does preexisting kidney damage diminish the elimination of plutonium from the body? Should persons with kidney damage be excluded from working with plutonium?

VI. Therapy

A. Development of methods of increasing elimination from the body

1. Effect of diet

2. Effect of injection of complexing or other agents

B. Methods of covering up material deposited in bone

C. Development of methods of therapy for plutonium in wounds (specific mention is made of those compounds mentioned under "diagnosis")

1. The effect of suction

2. The effect of increased venous flow

D. Formulation of a recommended procedure for treatment in case of a known overdosage by inhalation, by mouth, or by wound

E. How much time can elapse before treatment must be instituted?

VII. Protection

A. Is inactive dust in a work area an additional hazard in that it increases the probability of breathing plutonium?

B. Improvement of existing means of the physical protection of personnel from ingestion, inhalation, or direct inoculation of plutonium

C. Development of a method for the rapid determination of the quantity of plutonium in the atmosphere

D. Development of a continuous monitoring device for atmospheric or dust-borne plutonium which is effective in concentrations just above or at tolerance levels

E. Analysis of masks and respirators for percentage efficiency in filtering out various chemical forms of plutonium. Special mention was made of +4 and +6 nitrate, +3 and +6 sulfate, +3 and +4 chloride, +4, +5 and +6 carbonate.

F. Do various chemical structures play some part in the efficiency

of respirators or is particle size the important factor?

VIII. Plutonium-radium Ratios

A. What ratio for acute effects?

B. What ratio for chronic effects?

APPENDIX 2

Summary of Plutonium Cases

HP-1

White male, 67 yr, 70.3 kg.
Injected 10/16/45, 0.004 μCi/kg ^{239}Pu(IV) citrate.
Nine-year history of peptic ulcer, acute hemorrhage,
Hb = 13.7, RBC = 4.5.
Lost to follow-up.

HP-2

White male, 49 yr, 69 kg.
Injected 10/23/45,
Hemophilia, hypertension, cardiovascular disease.
Hb = 14.5, RBC = 4.1
Lost to follow-up.

HP-3

White female, 49 yr, 69.9 kg.
Injected 11/27/45, 0.0043 μCi/kg ^{239}Pu(IV) citrate.
Hepatitis, pruritic dermatitis with edema, hypoproteinemia,
Hb = 14.5, RBC = 4.3.
Follow-up 1645 days p.i., lost thereafter.

HP-4

White female, 18 yr, 55.5 kg.
Injected 11/27/45, 0.0054 μCi/kg ^{239}Pu(IV) citrate.
Cushing's syndrome, hypertension, nephropathy with uremia, osteoporosis.
Hb = 15.0, RBC = 5.3
Died 18 months p.i., autopsy withheld.

HP-5

White male, 56 yr.
Injected 11/30/45, ≈0.0044 μCi/kg ^{239}Pu(IV) citrate.
Amyotrophic lateral sclerosis, pneumonia, renal cysts and adenoma.
Died 151 days p.i., autopsied.

HP-6

White male, 45 yr.

Injected 2/1/46, ≈0.0044 μCi/kg ^{239}Pu(IV) citrate.

One-year history of Addison's disease, infected skin lesions.

Follow-up 523 and 1610 days p.i., lost thereafter.

HP-7

White female, 59 yr, 68 kg.

Injected 2/8/46, 0.0057 μCi/kg ^{239}Pu(IV) citrate.

Rheumatic heart disease, cardiac decompensation, toxic goiter, Hb = 12.6, RBC = 3.26.

Died 9 months p.i., autopsy withheld.

HP-8

White female, 41 yr, 54.4 kg.

Injected 3/9/46, 0.0073 μCi/kg ^{239}Pu(IV) citrate.

Two-year history of duodenal ulcers and scleroderma, Hb = 13.9, RBC = 4.7.

Lost to follow-up.

HP-9

White male, 66 yr, 63 kg.

Injected 4/3/46, 0.0061 μCi/kg ^{239}Pu(IV) citrate.

18-month history of muscular atrophy and dermatitis (dermatomyositis), Hb = 12.3, RBC = 3.9.

Died 456 days p.i., of bronchopneumonia, autopsied.

HP-10

Negro male, 52 yr, 71 kg.

Injected 7/16/46, 0.0053 μCi/kg ^{239}Pu(IV) citrate

Congestive heart failure, Hb = 13.3, RBC = 5.5.

Lost to follow-up.

HP-11

White male, 68 yr.

Injected 2/20/46, ≈0.0056 μCi/kg ^{239}Pu(IV) citrate.

History of chronic malnutrition and alcoholism.

Died 5 days p.i., cirrhosis of liver, edema, acites, autopsied.

HP-12

Negro male, 53 yr.
Injected 4/10/45, ≈0.0044 μCi/kg ^{239}Pu(IV) citrate.
Multiple comminuted fractures, Hb = 8.9, RBC = 2.85.
Biopsy 4 days p.i., lost to follow-up.
(Also designated E. C. in Ref. 18).

Chi-1

White male, 68 yr, 76.4 kg.
Injected 4/26/45, 0.0052 μCi/kg ^{239}Pu(VI) citrate.
Metastasizing buccal epithelioma, mild pyelonephritis,
Hb = 10.9, RBC = 3.56. Mouth surgery 2 days p.i.
Died 160 days p.i., autopsied.
(Also designated MX-100 in Ref. 48).

Chi-2

White female, 55 yr, 38.6 kg.
Injected 12/27/45, 0.15 μCi/kg ^{239}Pu(VI) citrate.
Metastasizing breast carcinoma and lymphoblastoma,
both tumors invading liver, kidneys, and bone marrow,
healing pathological rib fractures, Hb = 12, RBC = 3.5.
Died 17 days p.i., autopsied.
(Also designated WX-300 in Ref. 49).

Chi-3

White, male, young adult.
Injected 12/27/45, ≈0.085 μCi/kg ^{239}Pu(VI) citrate.
Hodgkin's disease, no other information.
Died ≈170 days p.i., autopsy withheld.
(Also designated as MX-200 in Refs. 49-53).

Cal-1

White male, 58 yr, 58 kg
Injected 5/14/45, 0.0896 μCi/kg ^{238}Pu, and 0.002 μCi/kg ^{239}Pu as $PuO_2(NO_3)_2$.
Diagnosed as gastric carcinoma, gastrointestinal hemorrhage,
Hb = 12, RBC = 4.1.
Biopsy 4 days p.i. revealed huge gastric ulcer and adhesions.

Total gastrectomy and splenectomy.
Followed for 340 days, died 1/9/66 (21 yr. p.i.) of cardiovascular disease.

APPENDIX 2, CONT'D

Case Cal-2[a]

This case, a 4-yr-10-mo-old white male of slight build, was suffering from osteogenic sarcoma with pathologic fractures. He was injected 4/26/46 i.v. with 0.169 μCi of ^{239}Pu(VI) nitrate, and tissue samples were obtained 7 days p.i. during a biopsy. Body weight was estimated to be 15.5 kg from Mühlmann's Tables[130] and Bayer and Bayley's curve[131] of retarded growth. Blood volume was estimated to be 7.5% of the body weight with a pcv = 0.4. Skeletal weight was estimated to be 2300 g, and the weight of the femora to be 0.125 of the skeletal weight from Theile's measurements[132] of children's bones. Died, 1/6/47, no autopsy.

Samples	Wet weight	% Dose	%/g
Cortex	4.05	0.237	0.0585
Tumor and adjacent trabecular bone	3.7	0.129	0.0349
Tumor adjacent to cortex	3.7	0.59	0.159
Calcified tumor and muscle	0.61	0.0285	0.047
Soft tumor and muscle	0.92	0.00085	0.00092
Periosteum	0.65	0.00056	0.00086
Plasma - 1 hr		5.78	0.0043
" - 4 days		.077	0.00063

Reconstruction of whole bone (femur)

$$\frac{(0.237 + 0.00056 + 0.129)\%}{(4.05 + 0.65 + 3.7)\ g} = \frac{0.372}{8.4} \qquad 0.0436\ \%/g$$

[a]Data of J. G. Hamilton, K. G. Scott, and B. V. A. Low-Beer, Unpublished.

APPENDIX 2, CONT'D

Case Cal-3[a]

This case, a 73.3-kg, 36-yr old Negro male, was diagnosed from biopsy as having an osteo-fibro myxochondrosarcoma involving the distal femur, patella and proximal tibia. He was injected 7/18/47 with 0.095 μCi ^{238}Pu(VI) nitrate intramuscularly at an ink-marked location on the gastrocnemius muscle. A mid-thigh amputation was performed four days p.i. Alive and well 7/17/68, 21 yr. p.i.

Samples	Wet wt. (g)	Ash wt. (g)	% of absorbed dose	% of absorbed dose/g
Tumor	29.5	0.37	0.60	0.0203
Bone and tumor[b]	31.5	12.6	0.144	0.0046
Marrow	4.0	0.05	0.063	0.0158
Normal cortex	50.5	20.0	0.063	0.00124
Muscle from normal bone	27.5	0.345	0.025	0.0009
Injection site	69.5	0.87	46.6[c]	

Whole femur reconstruction:

$$\frac{(\text{Bone + tumor}) + (\text{marrow}) + (\text{normal cortex})\%}{(\text{Bone + tumor}) + (\text{marrow}) + (\text{normal cortex})\text{g}} = 0.00313\%/\text{g}$$

[a]Data of J. G. Hamilton and J. C. Crowley, unpublished.

[b]Part of distal femur, patella, and proximal tibia.

[c]% of administered dose.

APPENDIX 3

Errors in original Pu source materials

Langham et al. (Ref. 19)

Table 5. HP-12 value for 1/6-day blood is probably 53 rather than 5.3 %.

This patient, also designated as E. C., was reported at four hours after injection to have "about 50% . . . . . still in the circulating blood".

Table 6. Urine in column 12 should read Chi-III; column 13 should read Chi-I; and column 14 should read Chi-II.

Table 6 (footnote 1). Should read, cases Chi-1, 2, and 3 received PuO_2^{++} in sodium citrate, Cal-1 received $PuO_2(NO_3)_2$.

Table 6 (footnote 1). Should read Cal-I received ^{238}Pu equivalent to 61 μg of ^{239}Pu.

Table 3, column 8. Make changes listed for Cal-1 shown below.

Crowley et al. (Ref. 57)

Page 2, lines 7 and 8. The original data sheets show the injected dose to have been 69,000 counts/sec of α particles. At counting geometry of 50% this would be 3.73 μCi of ^{238}Pu plus ^{239}Pu.

Table I, Column 5. Recalculated from the original data sheets, bone cortex should read 0.0072%/g and marrow should read 0.019%/g.

APPENDIX 4

Organ weights used to calculate total tissue plutonium content

	Adult male 70 kg, 174 cm		Adult female 58 kg, 162 cm	
Tissue[a]	Weight (g)	% body weight	Weight (g)	% body weight
Muscle	28,000	40.	17,000	29.3
Skin	4900	7.0	3500	6.0
Liver	1800	2.6	1400	2.4
Lung	1000	1.43	800	1.38
Large intestine	500	.72	500	.86
Small intestine	500	.72	500	.86
Heart	350	.50	300	.52
Kidneys	310	.44	260	.45
Spleen	180	.26	130	.22
Pancreas	100	.14	85	.15
Gonads	60	.09	10	.02
Thyroid	16	.02	14	.02
Adrenals	14	.02	14	.02
Lymph tissue	700	1.0	580	1.0
Skeleton[b]	10,200	14.6	7300	11.9

- -

[a]Soft-tissue weights and body proportions from ICRP Standard Man.[65]

[b]Skeletal weights and body fractions were calculated from dissections of 20 male skeletons: Bischoff,[73] one; Dursy,[74] two; Volkmann,[75] five; Mechanik,[66] eight; Mitchell et al.[76-78] four; and nine female skeletons: Bischoff,[73] one; Mechanik,[66] eight. The wet skeleton of ICRP Standard Man[64,65] includes a full set of teeth, articular and costal cartilages, periosteum, and marrow.

APPENDIX 5

Reconstruction of whole rib from divided samples. Original data were consulted and computational and typographic errors corrected.

Case No.	Sample	Pu conc (%/g)	Sample weight (g)	% dose in sample
Chi-1	Sternum	0.0047	4.38	
	Rib, cortex	0.0016	1.0125	0.0016
	Periosteum	0.0046	0.1215	0.00056
	Marrow & spicules[a]	0.0160	0.8292	0.0133
	Whole rib (calculated)	0.0079	1.963	0.0155
Chi-2	Rib, cortex	0.0210	0.43	0.0090
	Marrow	0.0196	0.2065	0.0040
	Whole rib (calculated)	0.020	0.6365	0.0013
Cal-1	Rib, cortex	0.0072	9.0	0.065
	Periosteum	0.0048	0.445	0.00216
	Trabeculae	0.0319	0.84	0.0269
	Marrow	0.0190	-	0.019
	Whole rib (calculated)	0.0081	14.0[b]	0.113

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[a]Origin of marrow sample noted as rib in Russell and Nickson (Ref. 47).

[b]Whole rib sample weighed before division into four separate samples.

APPENDIX 6

Wet weight of the human male skeleton and of the individual bones

Author	Volkman[75]		Mechanik[66]		Marei and Borisov[72]	
Location & date	Leipzig (1873)		Lenigrad (1926)		Moscow (1967)[a]	
No. of cases	5		6		7	
Mean age (yr)	47.6		41.5		43	
Mean body wt (kg)	56.6		61.9		Not reported	
	Wet wt (g)	% of total	Wet wt (g)	% of total	Wet wt (g)	% of total
Mandible[b]	112	1.4	141	1.7	132	1.2
Cranium[b]	808	9.8	848	10.2	1,193[c]	11.3
Humeri	493	6.0	547	6.6	596	5.6
Radii	136	1.6	153	1.8	390	3.7[d]
Ulnae	158	1.9	181	2.2		
Femora	1,528	18.6	1,493	17.9	1,635	15.5
Tibiae	888	10.8	886	10.6	1,185	11.2
Fibulae	174	2.1	166	2.0		
Patellae	52	0.6	58	0.7	71	0.7
Clavicles	72	0.9	80	1.0	91	0.9
Scapulae	224	2.7	253	3.0	360	3.4
Hands	222	2.7	232	2.8	277	2.6
Feet	591	7.2	629	7.5	677	6.4
Pelvis	897	10.9	808	9.7	1,193[c]	11.3
Ribs	568	6.9	615	7.4	655	6.2
Vertebrae	947	11.5	929	11.1	1,961[c]	18.6
Sacrum	282	3.4	238	2.8		
Sternum	74	0.9	76	0.9	147[c]	1.4
Total skeleton	8,226		8,333		10,563	

[a]Original tabulation was the average for 7 males and 6 females. These values were scaled up to males only, using male-female skeleton and bone relationships derived from the data of Mechanik[66] and Trotter and Peterson[86].

[b]Includes teeth.

[c]Dissection was apparently less thorough than those by anatomists Volkmann[75] and Mechanik,[66] and these samples probably include much more periosteum and cartilage.

APPENDIX 7

Distribution of Skeletal Burden of Various Radioisotopes in Man, Monkey, and Dog

	Percent of skeletal burden						
	Man		Monkey		Dog		
	^{226}Ra[b]	^{90}Sr[c]	^{90}Sr[d]	^{241}Am[e]	^{226}Ra[f]	^{241}Am[g]	^{239}Pu[h]
Head[a]	11.4	12.2	17.8	20.9	14.5	9.4	7.7
Vertebrae and sacrum	25.7	22.9	26.4	28.9	27.2	45.0	35.3
Sternum	9.0	1.8	2.7	1.5	4.5	6.0	1.8
Scapulae and clavicles		6.3	5.6	4.2	4.8	3.5	6.3
Ribs	11.3	13.4	6.4	5.9	10.6	8.5	11.7
Radii, ulnae, humeri	8.9	7.0	9.9	10.8	11.1	8.6	12.0
Femora, tibiae, fibulae	15.2	18.5	12.8	11.4	11.3	9.1	12.8
Pelvis	18.8	21.1	11.5	8.4	7.1	4.9	7.4
Hands and feet	7.8	8.5	5.4	6.2	6.8	2.0	2.4

[a] Includes teeth.

[b] Evans (Refs. 82, 83)

[c] Kulp and Schulert (Ref. 84)

[d] P. W. Durbin, M. H. Williams, and N. Jeung, unpublished. Adult rhesus monkeys (Macaca mulatta), No. 40F, 99 days p.i. and No. G8M, 2 days p.i.

[e] P. W. Durbin, M. H. Williams, and N. Jeung, unpublished. Eight adult female cynomolgus monkeys (Macaca irus philippensis) killed 1 to 63 days p.i.

[f] Atherton et al. (Ref. 79).

[h] Lloyd et al. (Ref. 80).

APPENDIX 8

Assessment of Errors in Calculation of Skeletal Pu from Eq. (3)

The ^{241}Am monkey studies provided material with which to assess the errors in Pu_{sk} calculated from Eq. (3). Eight female cynomolgus monkeys (Macaca irus philippensis) were killed from 1 to 63 days after an intravenous injection of ^{241}Am complexed with sodium citrate. Bones were dissected, cleaned of soft tissue, weighed fresh, and analyzed for ^{241}Am. The variations in body size and skeletal weights were small, respectively 10.4% and 13.7%.

$$\% \text{ error} = \frac{S.D._i \times 100}{i}$$

where i is the measured average, and $S.D._i$ is its standard deviation. The error in the fraction body weight skeletal weight was 11.4%. The errors in the weight fractions of individual bone groups were 10%, on the average. The errors in the calculated averages of the fractional bone distribution of ^{241}Am ranged from 6% to 20%. Individual variation of ^{241}Am uptake in the skeleton accounted for an additional error of 14% in the average skeletal ^{241}Am of the group. The combined error in skeletal ^{241}Am of an individual monkey based on a single bone calculation from Eq. (3) was of the order of 21%.* The total skeletal ^{241}Am of an individual monkey based on the average of several single bone calculations more closely approximated the measured value; if four bones were used the total error was reduced to ±8% of the measured value.

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*According to the theory of propagation of errors,

$$\frac{S.D.}{tot}\ tot = \left[\sum \left(\frac{S.D._i}{i}\right)^2\right]^{1/2}, \text{ and in this case}$$

$$\% e_t = \left[(11.4)^2 + (10)^2 + (15)^2\right]^{1/2}.$$

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CAPTIONS

Fig. 1. Pu loss from soft tissues (other than liver) after intravenous injection of Pu(IV) citrate or Pu(VI) citrate. Rat data are from Scott et al.[10] and Carritt et al.[62]; toxicity dogs were those of Painter et al.[14]; mongrel dogs injected with $Pu(NO_3)_4$ were those of Rysina and Erokhin[59]; beagles were those of Stover et al.[28].

Fig. 2. Disappearance of Pu from the blood of man, dog, and sheep. Dog data are from Stover et al.[28,29] all dose levels combined; sheep data are from McClellan et al.[38, 39].

Fig. 3. Rate of urinary Pu excretion by several Pu-injected persons, dogs and miniature swine. Swine data are from Clarke et al.[40]; dog data are from B. J. Stover and D. R. Atherton (original data, 0.1 μCi/kg and 0.3 μCi/kg groups only).

Fig. 4. Comparison of urinary excretion rates of four occupationally exposed persons and the rates predicted by the exponential Pu urine curve constructed in this paper (bold line) and the Langham equation[19] (dashed line). Occupationally exposed persons: ○--W.B.G., △--D.L.W., □--W.A.B.[19]; ◇--LASL-1, Foreman et al.[58]. Injected persons: ■--HP-3 and ▲--HP-6[19].

Fig. 5. Comparison with the normal Pu urine curve of urinary Pu excretion after an accidental exposure and treatment with DTPA. Data for RF-2075 were read from Figs. 1-6 in Lagerquist et al. ○--DTPA treatment two to seven times a week, ●--no DTPA treatment, •--no DTPA treatment values multiplied by 10.

Fig. 6. Rates of fecal Pu excretion by Pu-injected persons, dogs, and miniature swine. Dog data are from B. J. Stover and D. R. Atherton (original data) 0.1 μCi/kg and 0.3 μCi/kg groups only; swine data are from Clarke et al.[40].

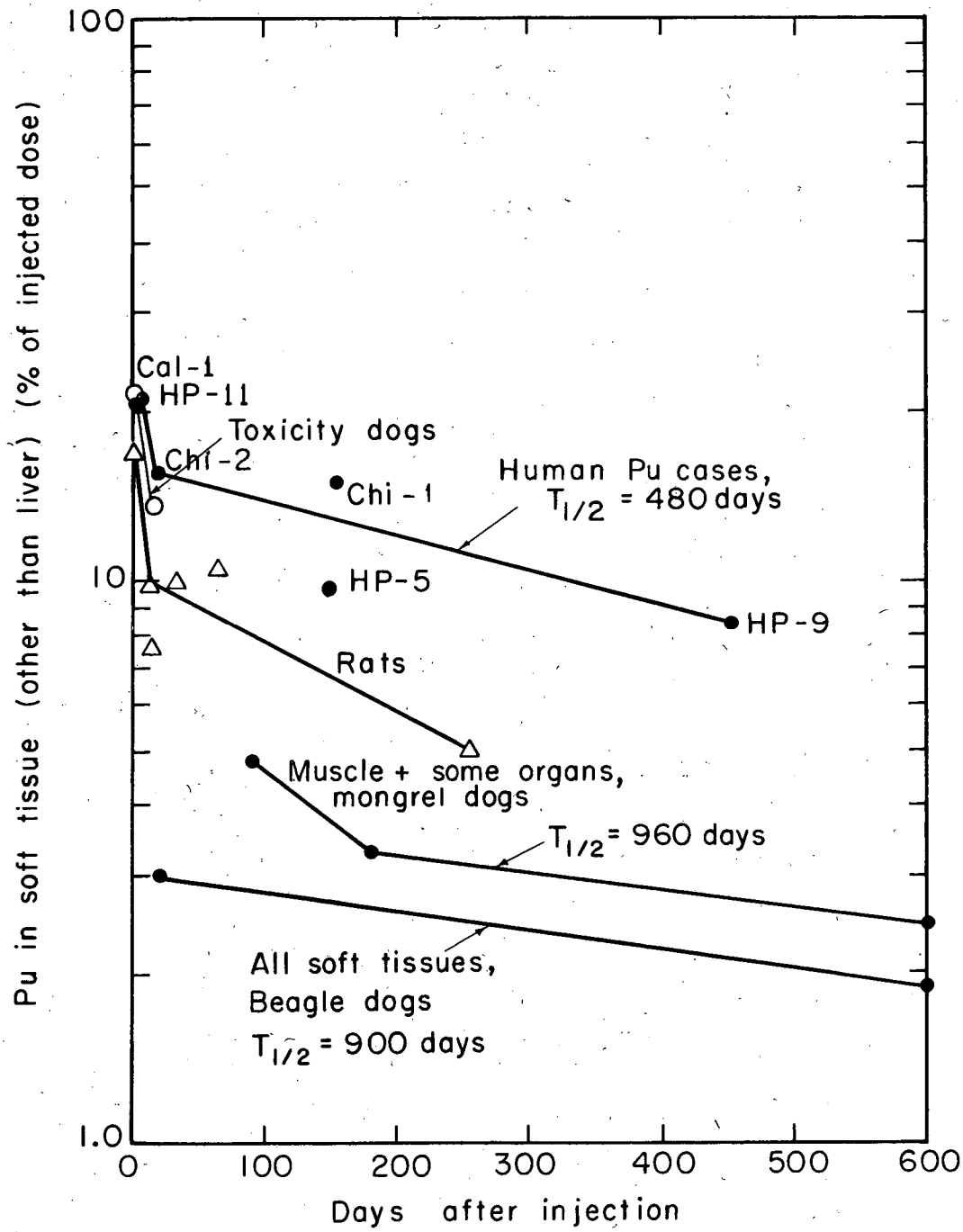
Fig. 7. Comparison of human urinary Pu excretion for from 1 day to 40 years predicted by the normal Pu urine curve with the Langham equation[19]. Points shown were calculated from the parameters in Table 10.

Fig. 8. Comparison of human fecal Pu excretion for from 1 day to 40 years predicted by the normal Pu fecal curve and the equation given by Langham et al.[19]. Points shown were calculated from the parameters in Table 14.

Fig. 9. Predicted whole-body content of Pu from 1 day to 40 years after intravenous injection during adulthood. Points shown were calculated from total excretion shown in Table 16.

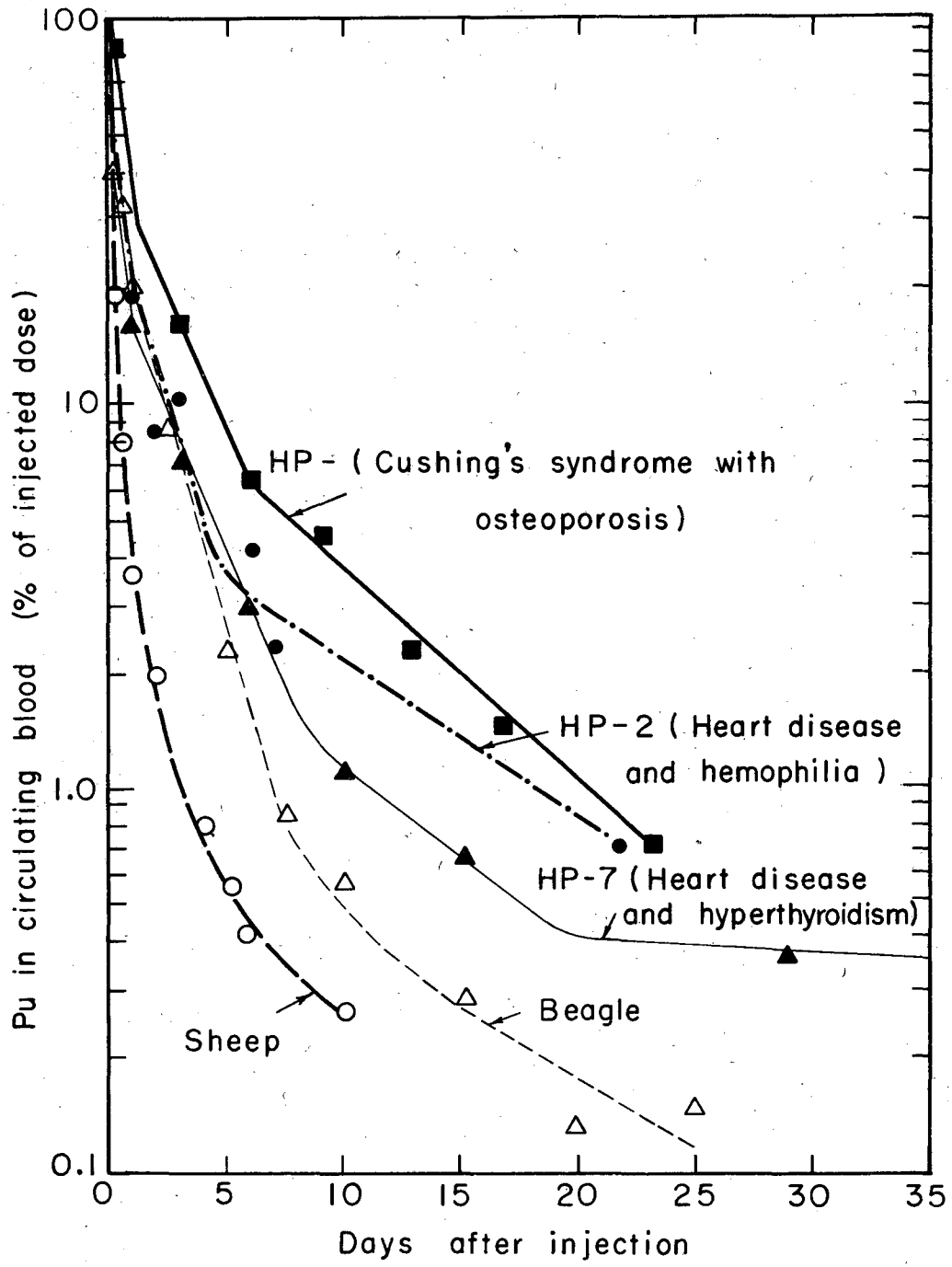
Fig. 10. Comparison of the percent of the Pu body content excreted daily in urine from 1 day to 40 years predicted by the normal Pu urine and fecal curves in this paper and the equations of Langham et al.[19]. Points shown were calculated from the parameters given in Tables 10 and 14.

Fig. 11. Predicted Pu content of the human liver following an acute exposure to Pu in soluble form.



XBL716-3737

Fig. 1



XBL 716-3736

Fig. 2

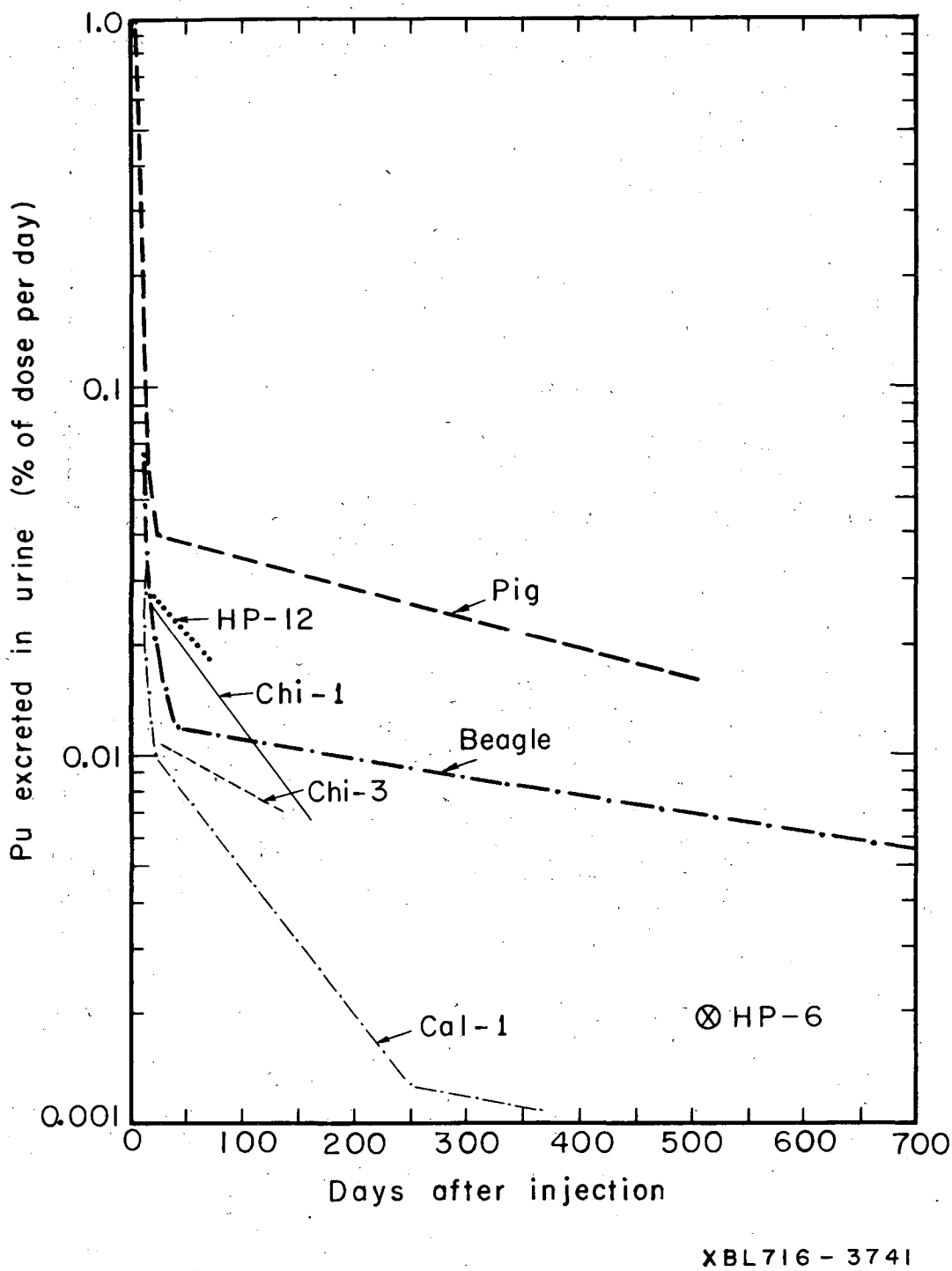

1.0
0.1
0.01
0.001
Pu excreted in urine (% of dose per day)
0
100
200
300
400
500
600
700
Days after injection
Pig
HP-12
Chi-1
Beagle
Chi-3
Cal-1
HP-6
XBL716-3741

Fig. 3

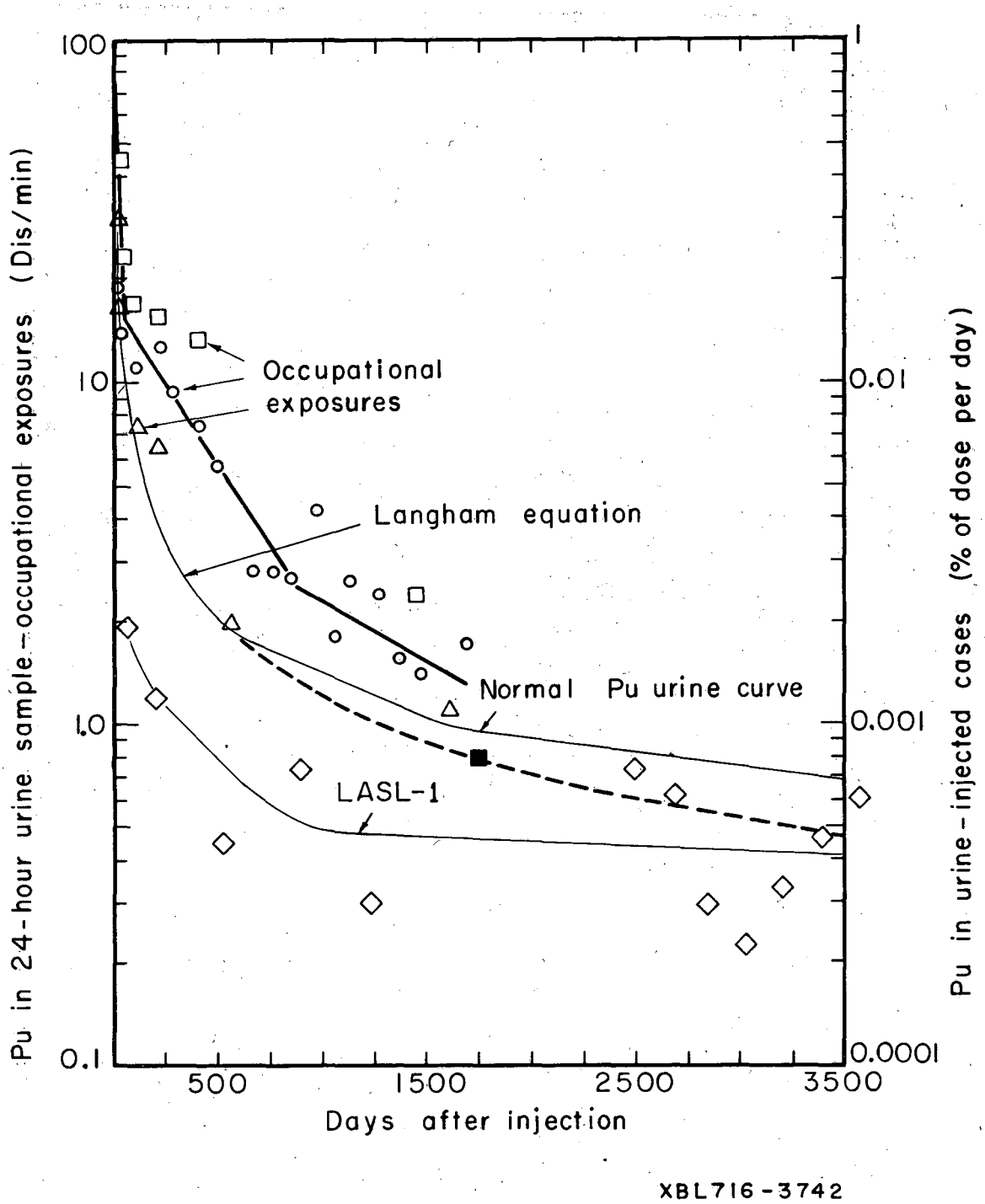

100
10
1.0
0.1
1
0.01
0.001
0.0001
500
1500
2500
3500
Days after injection
Pu in 24-hour urine sample-occupational exposures (Dis/min)
Pu in urine-injected cases (% of dose per day)
Occupational exposures
Langham equation
Normal Pu urine curve
LASL-1
XBL716-3742

Fig. 4

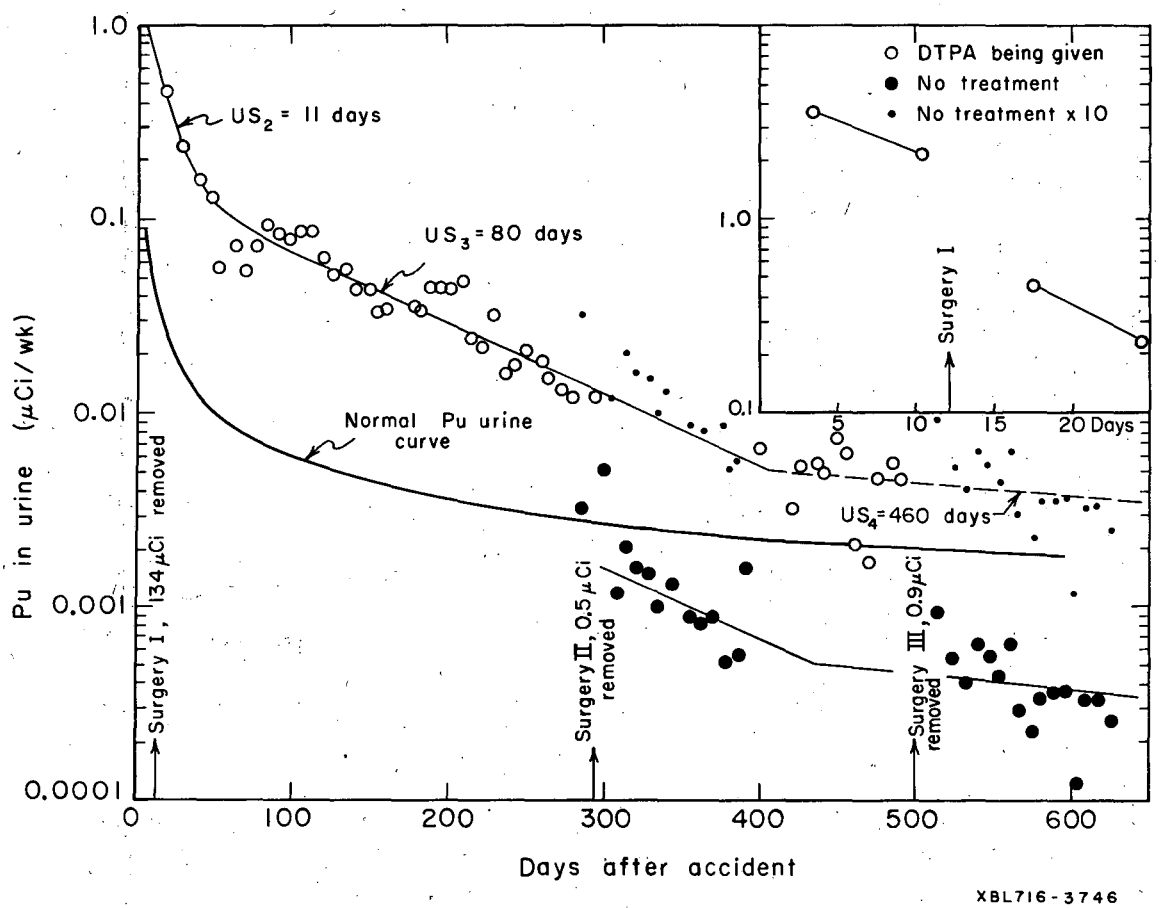
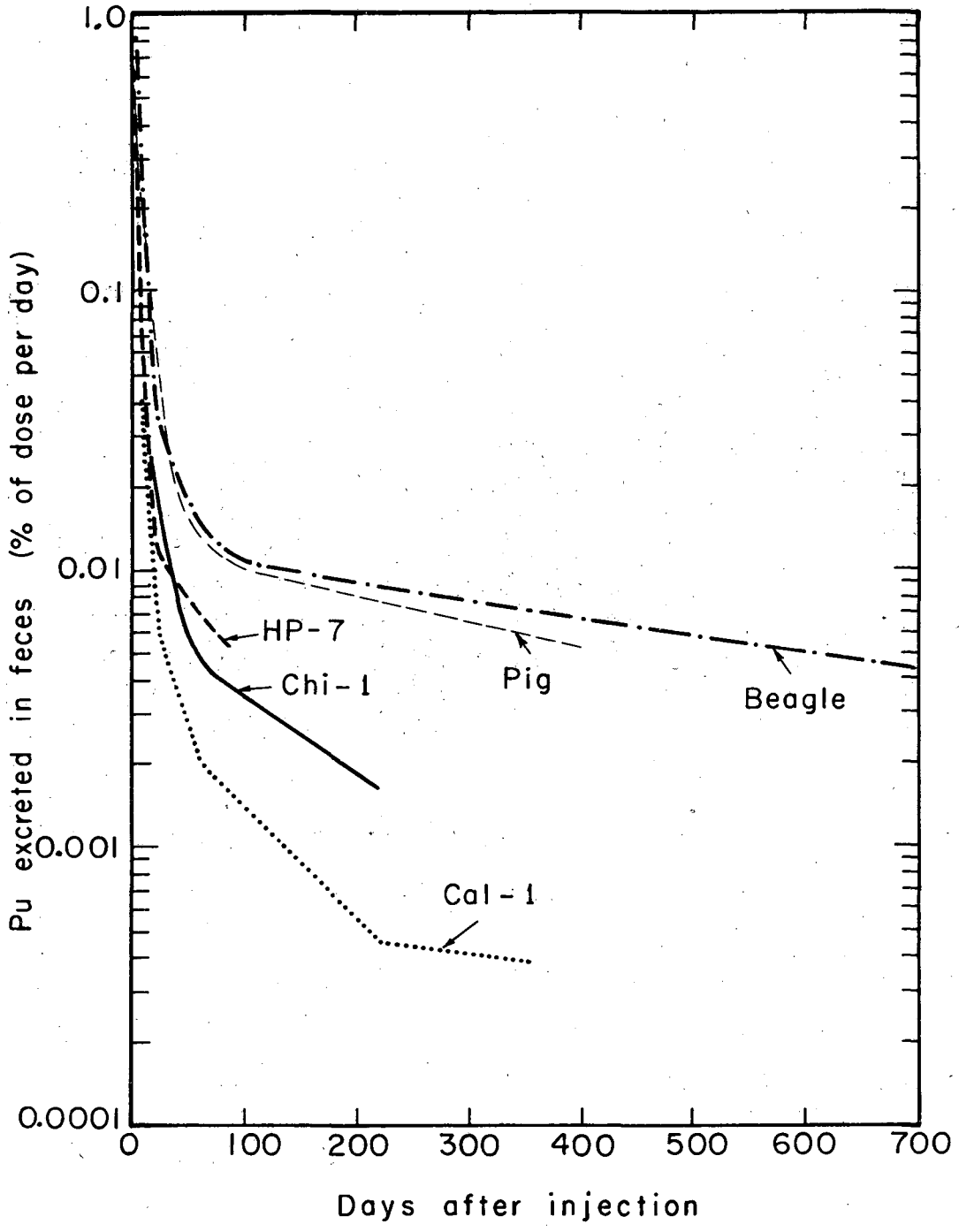

1.0
0.1
0.01
0.001
0.0001
Pu in urine (μCi/wk)
US2 = 11 days
US3 = 80 days
Normal Pu urine curve
US4 = 460 days
Surgery I, 134 μCi removed
Surgery II, 0.5 μCi removed
Surgery III, 0.9 μCi removed
0
100
200
300
400
500
600
Days after accident
DTPA being given
No treatment
No treatment x 10
Surgery I
5
10
15
20 Days
XBL716-3746

Fig. 5



XBL716-3740

Fig. 6

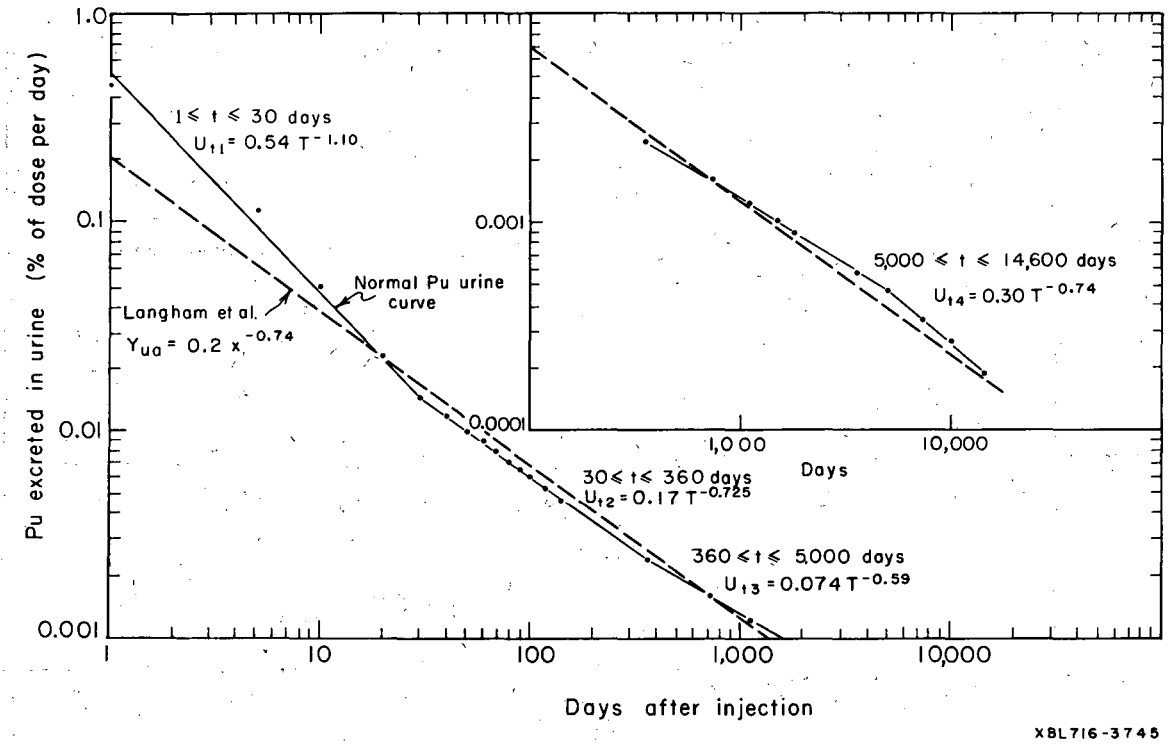

1.0
0.1
0.01
0.001
Pu excreted in urine (% of dose per day)
1 ≤ t ≤ 30 days
U t1 = 0.54 T^-1.10
Normal Pu urine curve
Langham et al.
Yua = 0.2 x^-0.74
30 ≤ t ≤ 360 days
U t2 = 0.17 T^-0.725
360 ≤ t ≤ 5,000 days
U t3 = 0.074 T^-0.59
0.001
0.0001
5,000 ≤ t ≤ 14,600 days
U t4 = 0.30 T^-0.74
1,000
10,000
Days
1
10
100
1,000
10,000
Days after injection
XBL716-3745

Fig. 7

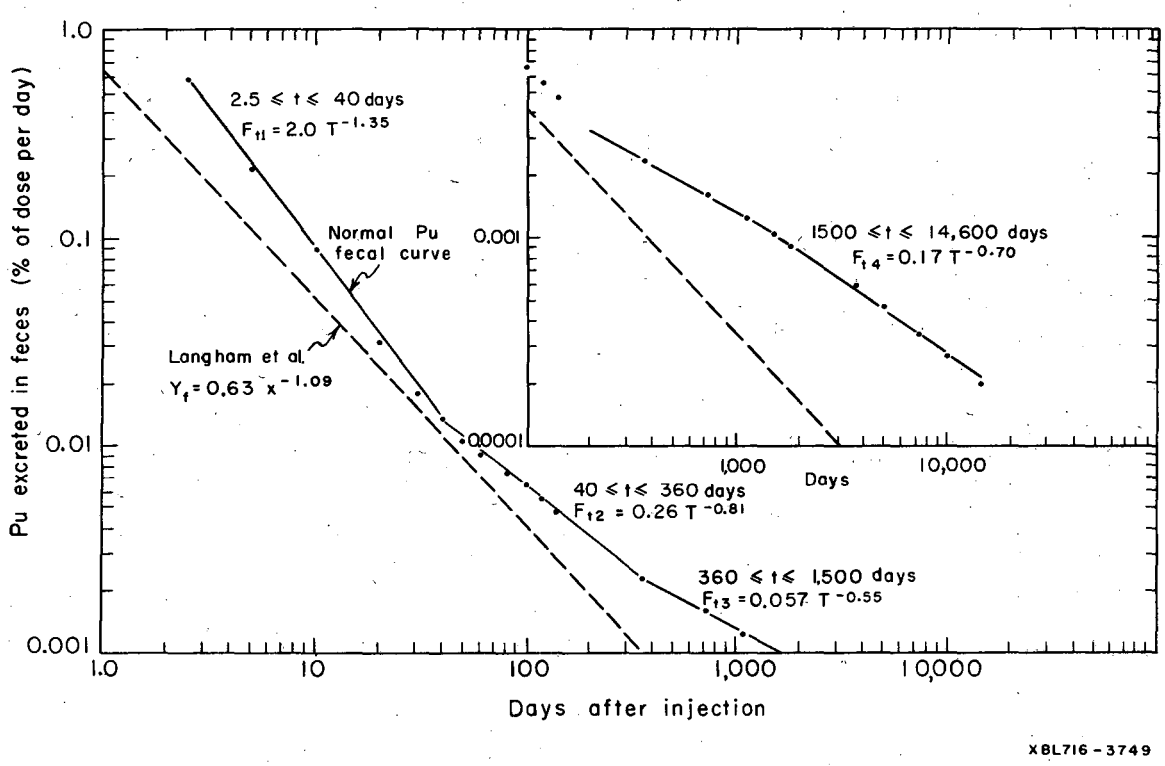

1.0
0.1
0.01
0.001
Pu excreted in feces (% of dose per day)
2.5 ≤ t ≤ 40 days
$F_{t1} = 2.0\ T^{-1.35}$
Normal Pu fecal curve
Langham et al.
$Y_f = 0.63\ x^{-1.09}$
0.001
0.0001
1500 ≤ t ≤ 14,600 days
$F_{t4} = 0.17\ T^{-0.70}$
1,000
Days
10,000
40 ≤ t ≤ 360 days
$F_{t2} = 0.26\ T^{-0.81}$
360 ≤ t ≤ 1,500 days
$F_{t3} = 0.057\ T^{-0.55}$
1.0
10
100
1,000
10,000
Days after injection
XBL716-3749

Fig. 8

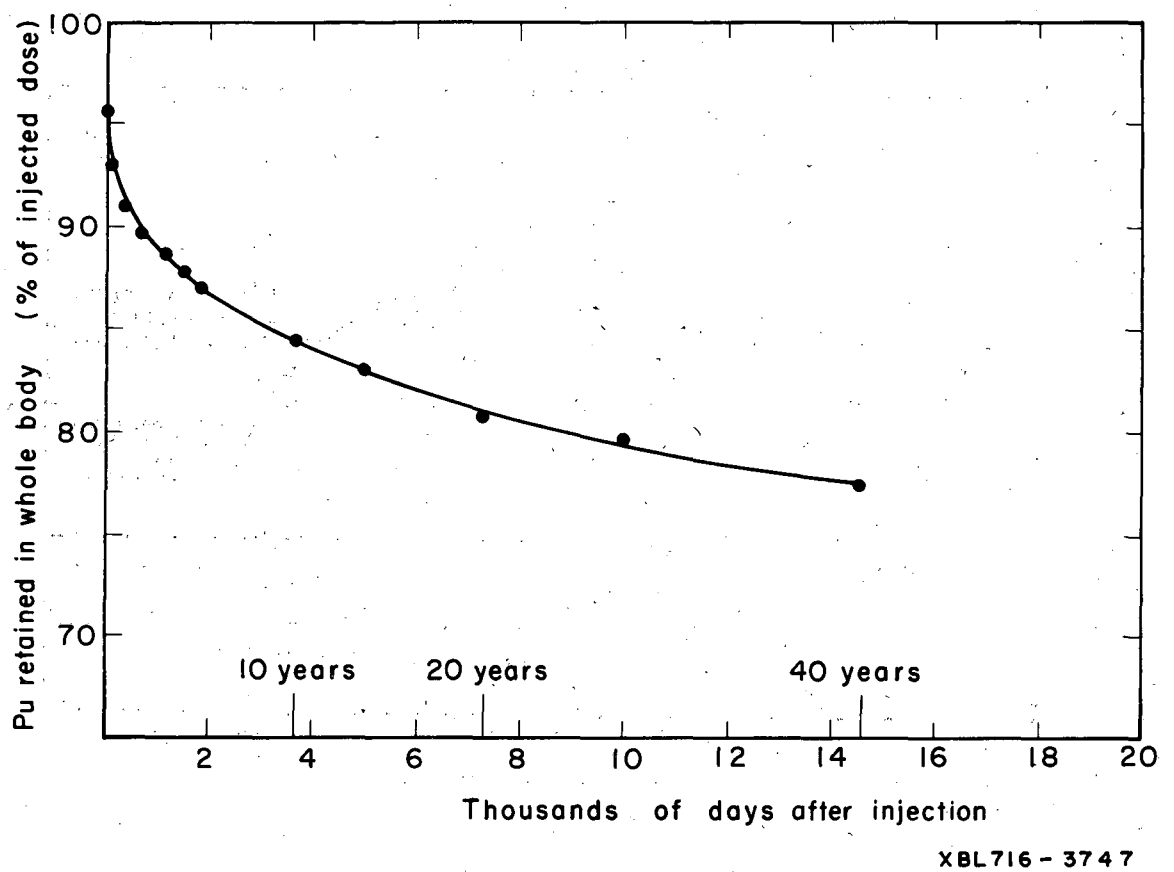

Pu retained in whole body (% of injected dose)
100
90
80
70
10 years
20 years
40 years
2
4
6
8
10
12
14
16
18
20
Thousands of days after injection
XBL716-3747

Fig. 9

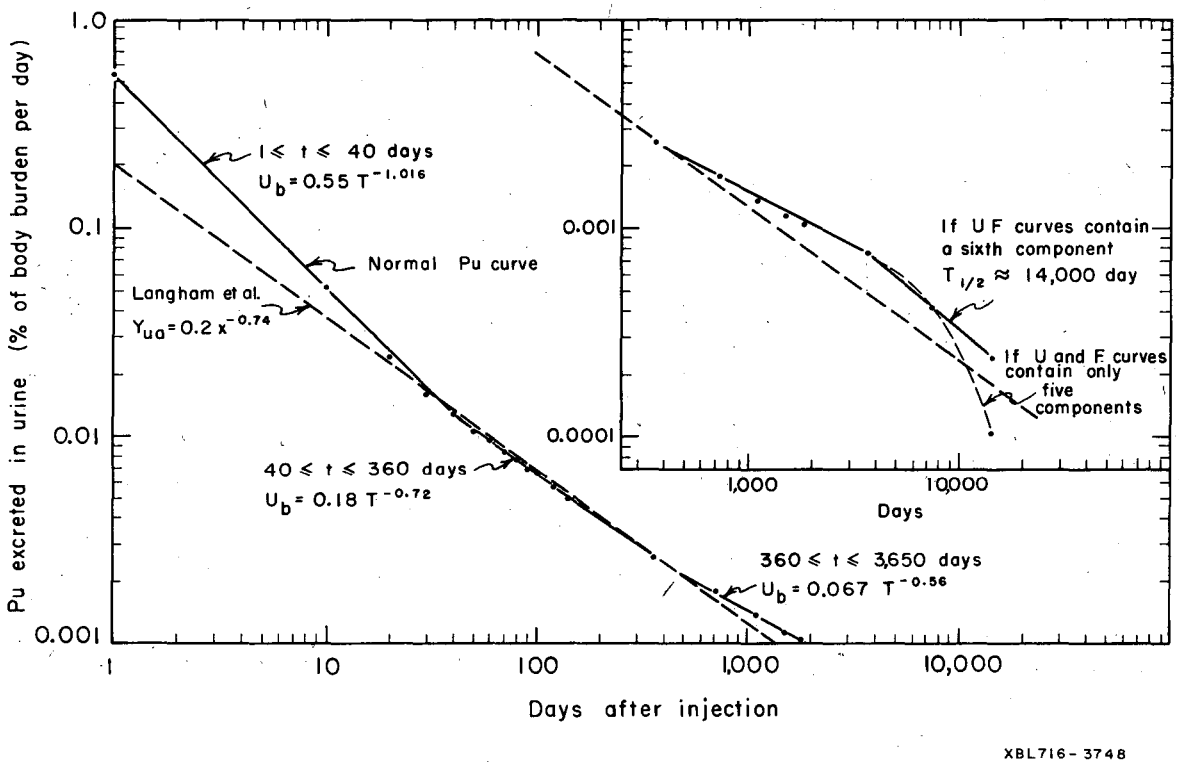

1.0
0.1
0.01
0.001
Pu excreted in urine (% of body burden per day)
1 ≤ t ≤ 40 days
$U_b = 0.55\ T^{-1.016}$
Normal Pu curve
Langham et al.
$Y_{ua} = 0.2\ x^{-0.74}$
40 ≤ t ≤ 360 days
$U_b = 0.18\ T^{-0.72}$
360 ≤ t ≤ 3,650 days
$U_b = 0.067\ T^{-0.56}$
1
10
100
1,000
10,000
Days after injection
0.001
0.0001
If U F curves contain a sixth component
$T_{1/2} \approx 14{,}000$ day
If U and F curves contain only five components
1,000
10,000
Days
XBL716-3748

Fig. 10

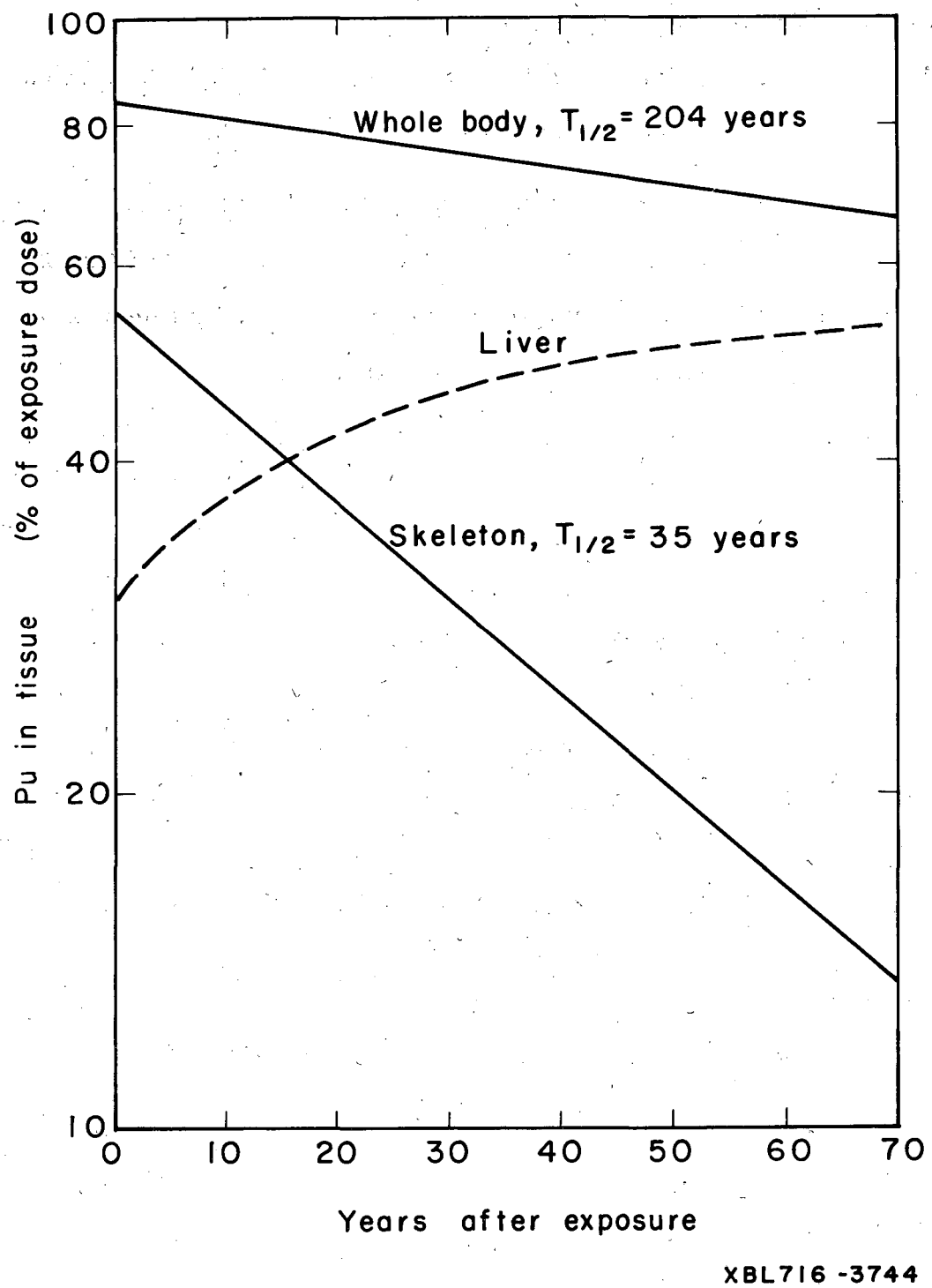

100
80
60
40
20
10
Pu in tissue (% of exposure dose)
Whole body, $T_{1/2}$ = 204 years
Liver
Skeleton, $T_{1/2}$ = 35 years
0
10
20
30
40
50
60
70
Years after exposure
XBL716-3744

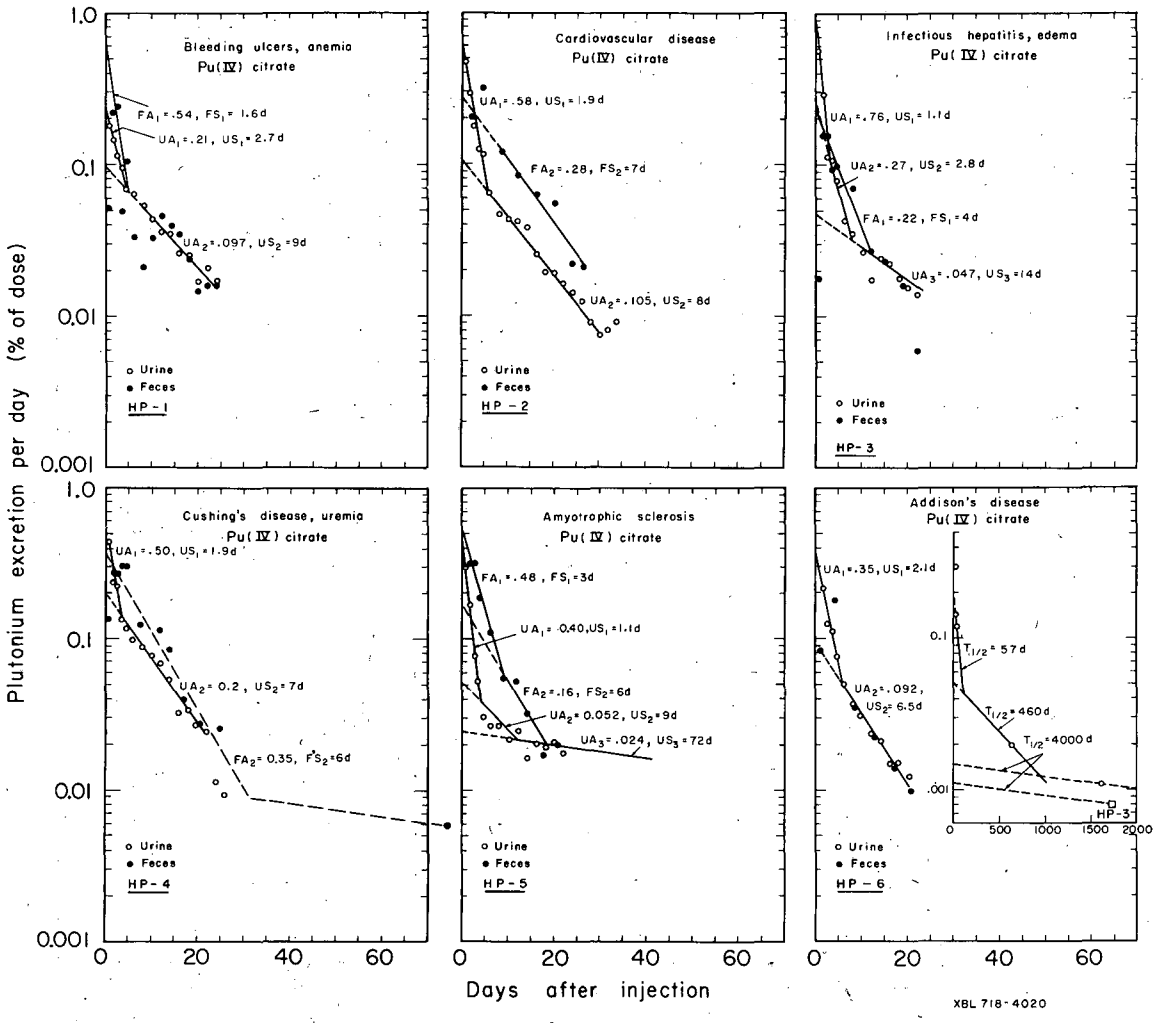
Fig. 11

Captions for Appendix Figures

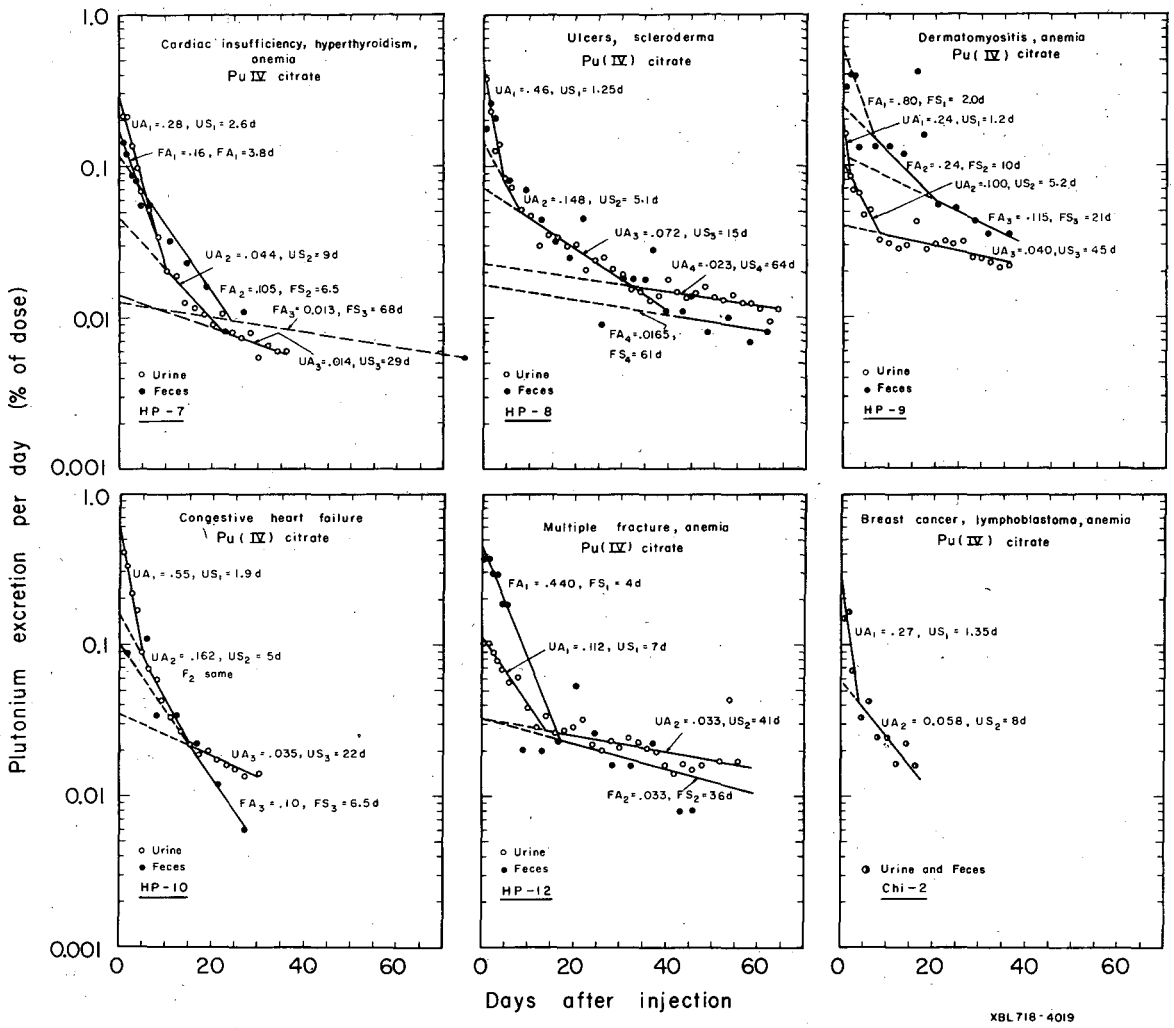
App. Fig. 9a. Urinary and fecal excretion of Pu by injection cases HP-1 through HP-6.

App. Fig. 9b. Urinary and fecal excretion of Pu by injection cases HP-7, HP-8, HP-9, HP-10, HP-12, and Chi-II.

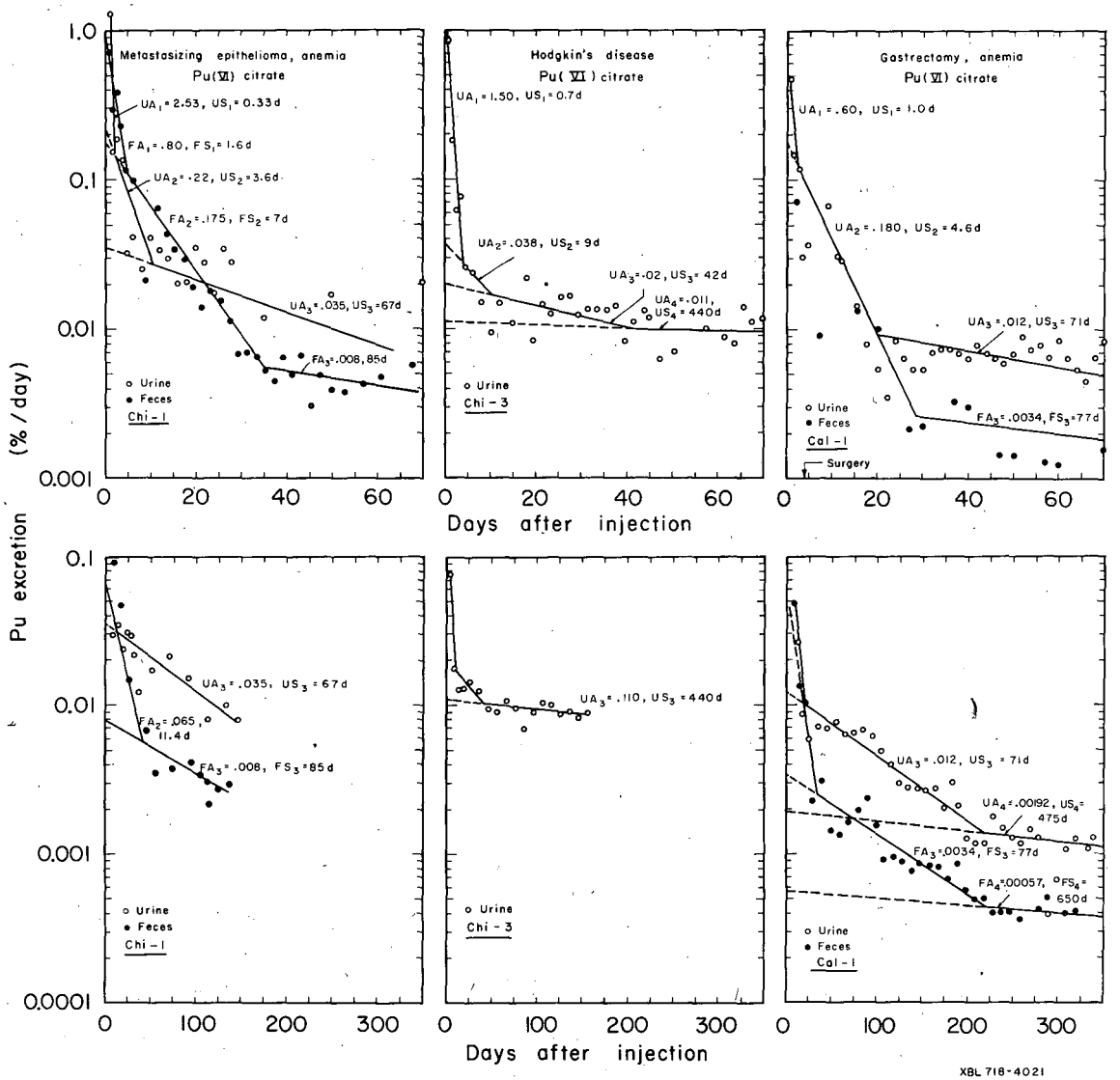
App. Fig. 9c. Urinary and fecal excretion of Pu by injection cases Chi-II, Chi-III, and Cal-1.



Appendix Fig. 9a



Appendix Fig. 9b



Appendix Fig. 9c

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